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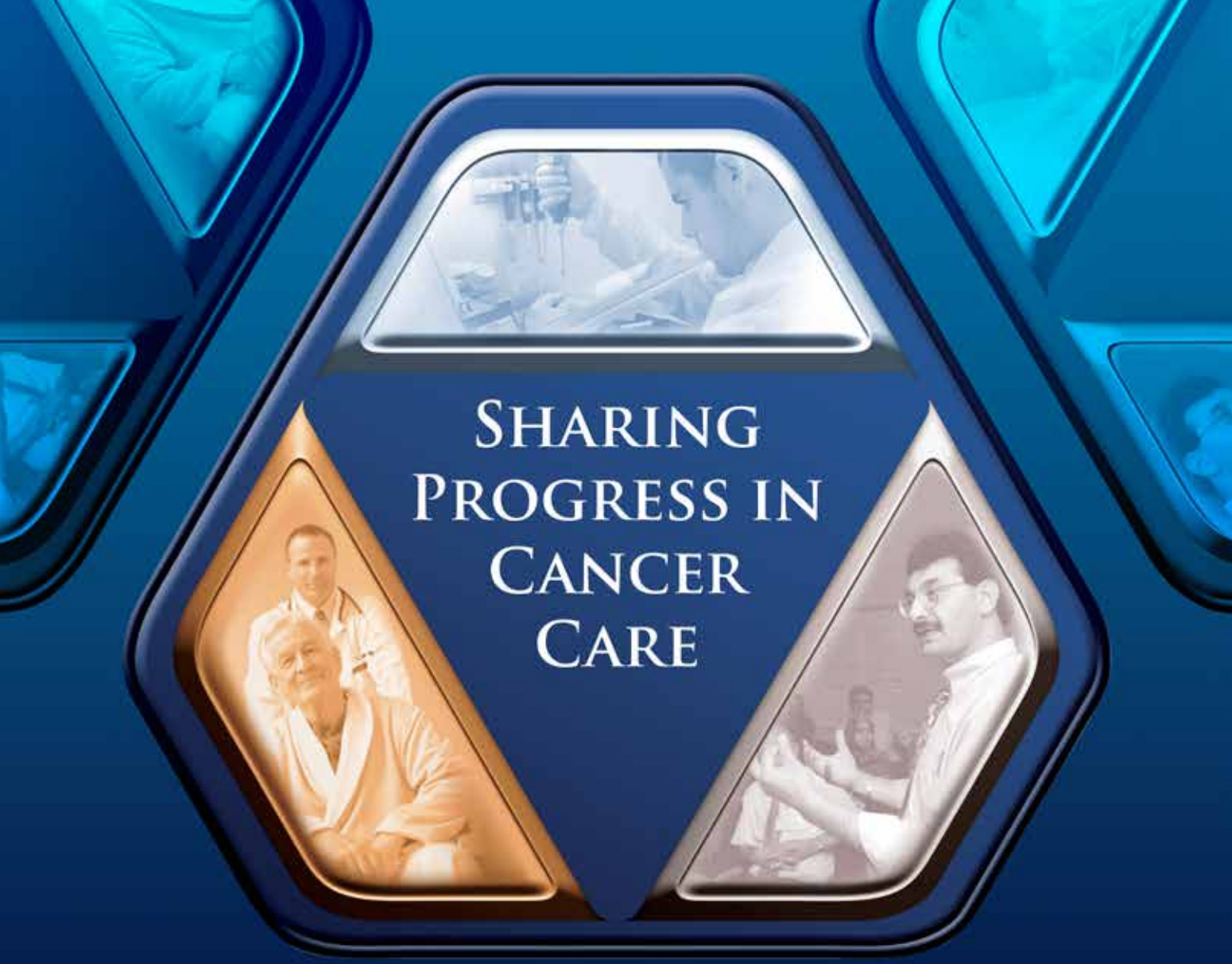

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*by **Vito Manolo Roma***

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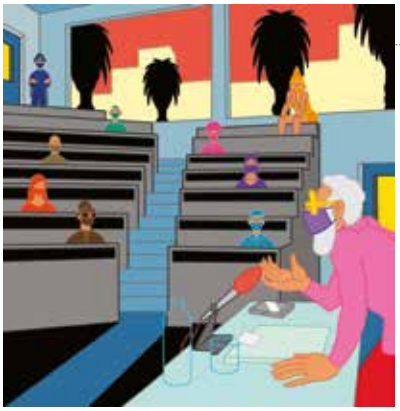


These COVID days

Adriana Albini *– Editor in chief*

'Tackling cancer in interesting times' was the theme of my first Editorial for *Cancer World*. I wrote that at the start of February this year, at a time when Europe remained largely oblivious to the implications of a new virus that had been wreaking havoc in parts of China. Within weeks, the spread of the pandemic, first to Italy and then across Europe, changed our lives as individuals and communities, in ways we had never foreseen. Currently it is hard to predict how long these 'interesting times' will continue, and what a new normal, when it comes, will look like.

These are testing times for the cancer community. For patients, above all, whose access to diagnostics, treatment and care has been hit in so many ways, and who have found themselves often isolated – in clinical consultations and in their daily lives – at a time when they most needed support. And for oncology professionals, trying to do their best while lacking the evidence to define 'best care' in the COVID setting, working within health systems often ill-prepared to deal with the high number of virus-infected patients, and at a time when social distancing made normal professional collaboration and patient care more difficult, and when many healthcare staff struggled with access to the personal protective equipment and testing needed to keep them and their patients safe.

These are indeed interesting times. But as I wrote in that Editorial, while the (purportedly Chinese) expression "May you live in interesting times" tends to be understood as a curse, evoking a sense of menace, it can also be seen as an invitation to consider the turn of human events in all their complexity.

This pandemic, this global tragedy and trauma, invites us to do just that. It invites us to ask questions about why we were so poorly prepared for this event, when the likelihood – even certainty – of a pandemic on this scale had long been predicted by scientists.

It invites us to count the cost of failing to invest in preventive measures – and to draw the conclusions and make the changes in the way we approach social issues: health, certainly, but also the environment, whose intricate connection with health has been demonstrated so catastrophically by this virus.

It invites us to value our health and care workers, who were initially left holding the frontline against this global threat, understaffed and underequipped, at a great cost to their health, mental health and too often, their lives. Not just with applause and media eulogies to their heroism, but with a pledge that never again should we require such sacrifice to deal with a threat that was foreseeable and foreseen.

It invites us to integrate into our new normal everything we've learnt about using information technology to communicate, collaborate and teach remotely, and about the value of interdisciplinarity – looking for answers among classic 'repurposed' or innovative molecules developed for other diseases; virologists and oncologists learning from one another.

And at a time when facemasks and social distancing are putting up additional barriers, it invites health professionals, not least in oncology, to identify closer with their patients, recognising that the sense of fear and vulnerability in the face of a disease that we don't fully understand, or know how to treat, or even how to avoid, is common to us all.

Cover image: We are nervous, behind our masks, yet determined to cure, still coming to medical school to learn the new lessons

© Vanni Cuoghi, 2020, "Without title and in silence", watercolor on paper

Delivering cancer care during the pandemic: lessons from the 'first wave'

As the COVID-19 pandemic shows signs of an autumn resurgence, **Anna Wagstaff** looks at how the 'first wave' impacted on the delivery of cancer care, and reviews responses to the *Cancer World* survey of clinicians on what went well, and what we need to do better.

"My partner had to be admitted to hospital with neutropenia earlier on in her treatment cycle, and she and I are constantly discussing what to do: whether we should ask about suspending treatment, how the risk/benefit equation adds up, whether we should call the consultant. But I think the fact is no one, not even COVID-19 experts, have the knowledge on which to base decisions. It's an evolving virus and an evolving pandemic: no one knows what to do."

These words were written in a chemotherapy clinic in England in early March 2020, around the time that new cases and deaths from the novel coronavirus were beginning to escalate in Italy, and the governments of Europe were sending out urgent public health warnings and preparing their citizens for lockdown (cancerworld.net/voices/covid-are-cancer-patients-being-protected/).

Over the following months, cancer services, and health services in general, would drastically change the way they operated, in line with the 'first do no harm' principle. Standard pathways and protocols were reviewed to ensure the benefit patients could expect was not outweighed by the added risk of being exposed to the virus and/or making them more vulnerable to infection or more likely to die if they caught it.

There were many reasons for concern. Cytotoxic drugs, some supportive drugs (such as steroids), and having cancer in itself are all known to impact the immune system, making people more vulnerable to catching an infection and limiting their ability to fight it off once caught. By contrast, immunotherapies are designed to boost the immune response, which led to fears of inducing cytokine storms in people exposed to the COVID-19 virus. Surgery is also known to repress the immune system for weeks or even months following an operation. The prevalence of comorbidities and older age that are common in cancer patients compound these risks further, leading to serious, potentially life-threatening symptoms from COVID.

In these circumstances, taking a very critical look at the risks versus benefits of inviting patients out of the safety of their homes to visit medical facilities, and administering treatments that could raise their risk from COVID, was clearly the right thing to do. All the more so, where those same medical facilities were also treating patients with COVID, and at a time when no reliable COVID testing was available and many hospitals were struggling to get basic protective supplies, such as hand sanitizer and personal protective equipment (PPE), needed to keep themselves and their patients safe.

Risks and benefits – the clinicians perspective

The only published evidence available at that time came from China. A case series report from the Chinese Center for Disease Control and Prevention (Wu Z and McGoogan J *JAMA Netw* 2020) showed a case fatality rate from COVID of 5.6% among cancer patients compared with 2.3% for the general population. A prospective study from the Chinese National Clinical Research Center for Respiratory Disease (Liang W et al. *Lancet Oncol* 2020) reported on a cohort of 1,590 patients with COVID, which included 18 people who had cancer or had recently been treated for cancer, of various types, at various stages and with various treatment modalities. The data indicated that people with cancer were much more likely to die or need invasive ventilation than people without cancer, even after accounting for age, smoking history and other comorbidities. Among cancer patients, those who had received chemotherapy or surgery in the past month were more likely to experience clinically severe events than those who had not been treated in that timeframe.

It would be several months before data from much larger studies became available, which started to tease apart which cancer patients were most at risk from severe events or death, and importantly questioned the finding that cancer treatment per se – using any modality – increased the risk of severe events or death from COVID (Kuderer NM et al. *Lancet* 2020; Lee LYW et al. *Lancet* 2020). Meanwhile, oncologists had to act on the evidence available, which in hindsight may have led to undue caution, as was recognised in the consensus paper on 'Managing cancer patients during the COVID-19 pandemic', published at the end of July 2020 by the European Society for Medical Oncology (Curigliano G et al. *Ann Oncol* 2020).

The general policy widely advocated early on was to continue treating patients already in treatment, but to consider adjusting the standard treatment to protocols that were deemed safer in terms of the risk from COVID. This included moving to longer treatment intervals for chemotherapy, shifting

from hospital-administered infusions to oral treatments that could be taken at home, avoiding immunotherapies, abbreviating radiotherapy courses, or giving fewer but higher doses, cancelling follow-up visits or conducting them remotely, and possibly delaying the start of adjuvant treatment.

When it came to new patients, the question was whether to wait until the 'first wave' of COVID was over before starting treatment. In a lot of cases, that is exactly what happened. Considerations of the best interests of the patient were not the only driver here, but they were important. While immediate treatment is imperative with certain cancers, there are others where a few weeks' delay poses little additional risk, and given the evidence from China it made sense to weigh the relative risks carefully for each patient.

The lack of detail in that evidence, however, made the balancing exercise harder. Was chemotherapy the biggest threat? Should neoadjuvant treatment be omitted in favour of wider surgical excision? Or was surgery the biggest threat? Should patients be kept on neoadjuvant treatment for longer than normal to keep the cancer under control until the COVID spike had passed, when surgery could be performed more safely? How much does each week of delay impact on the effectiveness of surgery or of adjuvant therapies, and in whom?

Oncologists are used to working with unknowns, but this was truly unprecedented territory – a once-in-a-generation challenge – where every evidence-based guideline that could be trusted as the gold standard before COVID could no longer be assumed to apply.

The global cancer community was quick to collaborate on national and international registries to start developing the much-needed evidence as fast as possible. But it wasn't until May 2020 that the first publications began to come out. In the meantime, oncologists had to look for guidance that started coming out of leading cancer services, cancer centres and professional organisations, based on the limited available evidence together with basic principles and common sense – and usually accompanied by the caveat "these are not guidelines".

Risks and benefits – the patients' perspective

In some cases the decision to interrupt treatment was initiated by patients. Powerful messaging from governments about the dangers of COVID aimed to maximise population-wide compliance with the lockdown, rather than to equip cancer patients with the information they needed to weigh up the risks of catching COVID against the risks of interrupting their care. Messaging from oncologists and patient advocacy groups stressed the higher risk COVID posed for cancer patients and the importance of 'shielding' – staying away from all possible sources of infection. And they could not count on hospitals to be safe.

While cancer centres were usually safer than oncology units within general hospitals, reaching them often involved longer journeys, which was either risky or sometimes impossible by public transport. Stories about COVID outbreaks in hospital units treating non-COVID patients hit the headlines, and fuelled public fears that medical facilities were risky places.

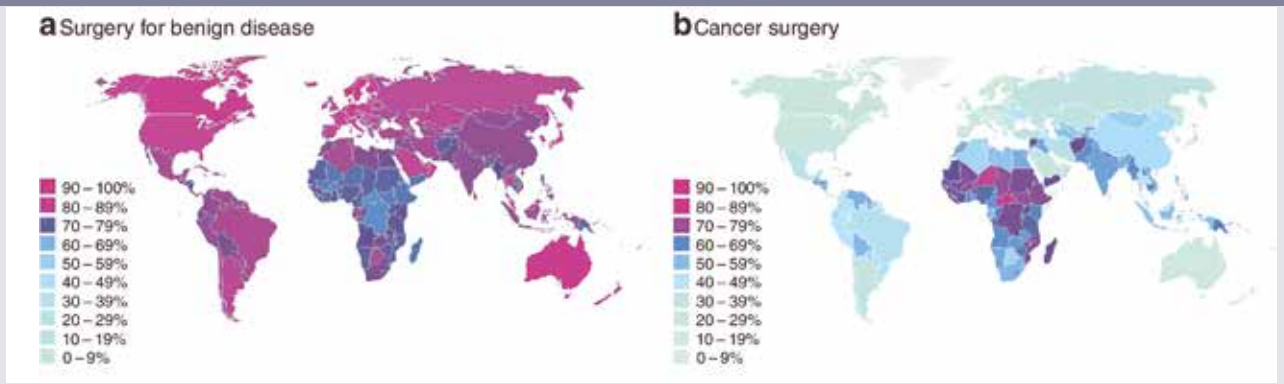
One melanoma patient advocate in France described the feeling in the patient community: "When they hear that there is no PPE or triage, that healthcare professionals are overstretched, and they are more vulnerable, say, to cytokine storm, they then have to decide whether being constantly worried about progression not being picked up is really worse than risking COVID… Some go in looking like Buzz Aldrin, and others stay at home and cancel."

Cancer patient advocacy groups reported receiving double the average number of calls compared to pre-COVID days, with more than four out of five of the queries relating to COVID concerns (bit.ly/cancer-advocacy-covid-survey). Not surprisingly, almost nine out of ten respondents to a survey of affiliates conducted by five global cancer advocacy coalitions reported worrying levels of stress and anxiety among patient communities, with many reporting a significant impact on attending medical appointments.

Capacity and priority

Other pressures were at work, which arguably had as great an impact on the delivery of cancer care. Chief among them was health service capacity. Available data on the per capita number of beds and intensive care beds, for instance, indicate massive disparities across Europe. Germany has up to three and a half times as many hospital beds per capita as countries such as Portugal, Italy, Spain, the UK and Sweden (Eurostat, bit.ly/EUROSTAT-hospital-beds,

Expert estimates of surgeries cancelled or postponed during the 12-week peak disruption



In this predictive modelling study, best estimates for country-level postponement/cancellation rates for cancer surgery, during the 12-week peak disruption, across 71 countries, ranged from 23.4% to 77.1%, with estimates for European countries being in the lower range

Source: COVIDSurg collective (2020) Elective surgery cancellations due to the COVID-19 pandemic: global predictive modelling to inform surgical recovery plans. *Br J Surg* 107:1440-1449. © 2020 BJS Society Ltd Published by John Wiley & Sons Ltd. Republished with permission

accessed 23 Sept 2020). Its intensive care bed capacity is between two and and three times that available in Italy and Spain, around four or five times that available in the UK and Sweden, and almost seven times that available in Portugal (Rhodes A et al. *Intensive Care Med* 2012).

Many health services struggled too with their staffing levels, in some cases redeploying medical and non-medical staff from oncology and other units, which were already suffering from high levels of absence due to COVID infection or 'self-isolation'. All over Europe, elective surgeries were delayed or cancelled, as all available capacity was prioritised for COVID patients.

Collateral damage: cancellations, delays and changed protocols

Cancer diagnosis

The disastrous drop in diagnosis and referrals of new cancer cases across Europe will no doubt prove to be where the pandemic wrought the greatest collateral damage (*Cancer World* published online 21 May 2020). Interruptions in screening programmes, delays in diagnostic referrals, and public reluctance to contact medical services about worrying symptoms were all contributing factors. One modelling study estimated that, in the UK alone, around 3,500 people in the UK will die from breast, colorectal, lung and oesophageal cancers who could have been cured if diagnostic routes had been working as normal, amounting to around 60,000 years of life lost (Maringe C et al. *Lancet* 2020). Such reports have led to calls for a change in policy to ensure all diagnostic referrals – not just those where cancer is strongly suspected – continue as a priority during this and any future pandemics, and for clear public messaging about the importance of moving quickly to get checked out if people have symptoms that they are concerned about.

Cancer care

The impact on patterns of treatment and care has been harder to quantify. To try to get a snapshot of what was happening at hospitals and cancer centres across Europe, *Cancer World* conducted a survey of oncologists in early June 2020, on 'Cancer Care During the Pandemic: Problems and Solutions' (bit.ly/CW-COVID-survey). The survey asked questions regarding concerns about delays in diagnostics and treatment, changes to standard practice, approaches to clinical decision making, communication with patients and colleagues, and safety issues. Some respondents were contacted again in mid-August 2020 to get more detail, or updates, on their comments to the original survey.

Responses to the survey indicate that, in most European countries, changes to normal pathways and protocols happened in around four out of ten patients. The reported proportions increased to around six in ten in some countries, including

Belgium and the UK, but were lower in others, including Switzerland and Germany. Changes to the normal course were reported to be slightly more frequent in general hospitals than cancer centres.

This finding concords with a comment made in response to the survey by a practitioner at a leading southern European cancer centre, indicating that the realities at that cancer centre were very different to those at the majority of hospitals treating cancer patients elsewhere in the country. In France, a melanoma patient advocate reported that, while the Institut Gustave Roussy cancer centre seemed to be operating "relatively normally", in other places significant changes to care were happening, with patients being switched from immunotherapy to targeted treatments and transfers to clinical trial centres being put on hold.

The *Cancer World* survey was circulated just around the time that some of the stronger evidence was emerging that suggested sticking to standard protocols for medical treatments was safe in many patients, and the survey would not have reflected that new information. However – with some notable exceptions – responses did indicate confidence (7 on a scale of 1–10) that, in the changed pandemic environment, most oncology teams were making an effort to tailor treatment and care plans to each patient's individual risks, benefits and preferences, and that the implications of any changes or delays to standard treatments were generally discussed with patients (7 on a scale of 1–10). Confidence levels about whether treatment recommendations were made following multidisciplinary team (MDT) discussions were lower (just over 5.5 on a scale of 1–10).

Guidelines: Of the 30 European countries represented by respondents to the *Cancer World* survey, the great majority said they had some form of national guidelines as well as hospital guidelines. Countries with strong professional oncology organisations were able to rapidly translate emerging evidence into recommendations and best-practice guidance. Where that lead was lacking, however, the guidelines seemed to be driven more by protecting against the risk of COVID than ensuring cancer patients got the treatment they need. An oncologist in Bulgaria commented that, in the early stages, "There were many national recommendations [that were] contradictory and changing from day to day… The instructions were to minimise the risk of a COVID patient entering any hospital system." In practice, this meant that any patients with fever were immediately referred to COVID units, "regardless of their other diseases or need of treatment".

"During the COVID era, the first problem to be excluded is a viral infection. This introduces a delay, a need for a second consultation, stress and at least two visits to the hospital of patients who are frequently in a poor condition."

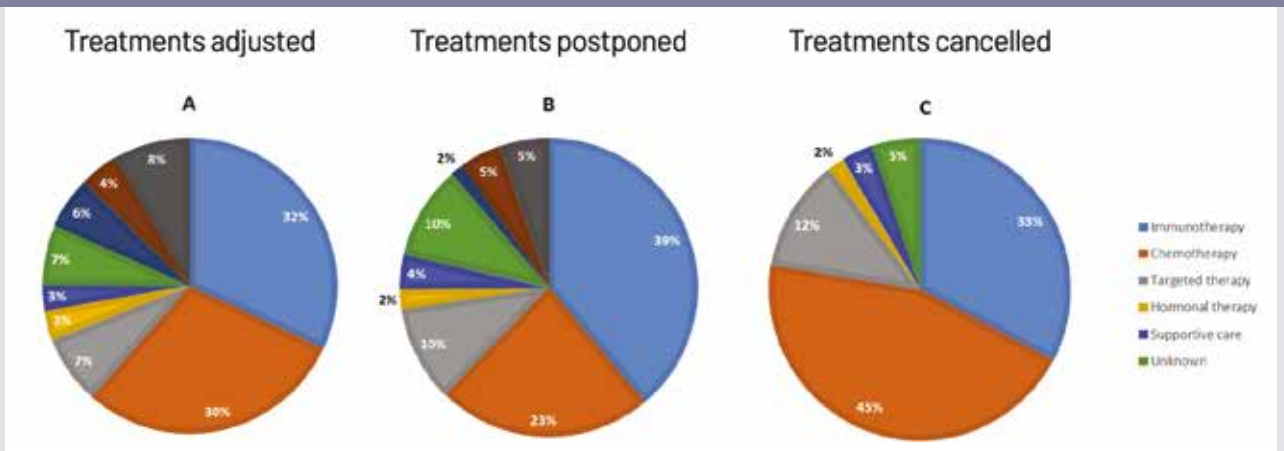
With time, and as more evidence and guidance emerged at an international level, the oncologist adds, "we learned how to manage these patients and to minimise the stress both for them and for us." But given the weakness of the national oncology lead, six months into the pandemic many oncologists in Bulgaria were still reportedly reluctant to treat patients for fear of the COVID risk. "This has led to a transfer of many patients to colleagues who 'take the risk' to treat the cancer disease from other colleagues who 'prefer to stay on the safe side'."

Even in countries with strong professional oncology guidelines, differences in implementation by region or from hospital to hospital have been reported.

In the UK, for instance, where the NHS and the National Institute for Health and Care Excellence (NICE) were quick to develop and publish national guidelines during the pandemic, such as on the delivery of systemic anti-cancer treatments, variations in practice have been reported. In their response to the survey of affiliates conducted by five global cancer advocacy coalitions, a UK group commented that, in "some parts of the UK", women with ovarian cancer had had "significant non-evidence based changes to the treatment pathways, e.g. no chemotherapy for women with platinum-resistant disease, lack of access to counselling services and palliative care," (bit.ly/cancer-advocacy-covid-survey). Such reported variations may reflect local differences in COVID prevalence and/or health service capacity, or simply the difficulties of responding at speed to a rapidly changing evidence base.

Cancer surgery: A predictive modelling study conducted by the COVIDsurg collaborative, and based on expert assessments, estimated the cancellation rate for cancer surgery during the 12-weeks of peak disruption would range from almost one in four to more than

Changes to standard treatments during the pandemic, by modality



In an online survey conducted in the Netherlands in April 2020, one in five patients indicated their treatment had been adjusted, postponed or cancelled. The pie charts show the breakdown of these changes by treatment modality

Source: K. de Joode et al (2020) Impact of the coronavirus disease 2019 pandemic on cancer treatment: the patients' perspective. *Eur J Cancer* 136:132–139 © Elsevier 2020. Reprinted under a Creative Commons Licence

three in four across the globe, with most of Europe being at the lower end of the range (COVIDSurg collective *Br J Surg* 2020). The authors called on governments to "mitigate against this major burden on patients by developing recovery plans and implementing strategies to restore surgical activity safely."

Responses to the *Cancer World* survey indicated that concerns over delays and cancellations were higher with respect to surgery than any other elements in the cancer pathway, except for diagnostics (bit.ly/CW-COVID-survey). Many respondents highlighted their concerns over potentially curable cancers moving to higher stages and becoming inoperable. They also queried the evidence basis for the delays, "There is not clear evidence that delays may protect patients from COVID but it is likely that they may affect the outcome."

Among survey respondents, German oncologists were the only ones to report no disruption to cancer surgery. (By contrast, "practically no scheduled follow-up of cancer patients after completion of their treatment was performed," commented one surgeon from Berlin, who voiced fears of "significant delays in the diagnosis of metastasis/recurrence".)

A UK study published in mid-May, based on age-specific and stage-specific cancer survival for England between 2013 and 2017, calculated that delaying cancer surgery by three or six months would result in the attributable deaths of, respectively, 4,755 or 10,760 people who would otherwise have achieved long-term survival (Sud A et al. *Ann Oncol* 2020). The message from the authors was, "to avoid a downstream public health crisis of avoidable cancer deaths, cancer diagnostic and surgical pathways must be maintained at normal throughout, with rapid attention to any back log already accrued."

Medical treatments: Some indication of the extent and nature of changes to medical oncology treatments is offered by a survey of patients in the Netherlands conducted by the Dutch Federation of Cancer Patients Organisations over three weeks beginning 28 March 2020 (de Joode K et al. *Eur J Cancer* 2020). Among the 2,664 respondents who had had contact with the hospital, one in five indicated their treatment had been changed (i.e. adjusted, delayed or discontinued). In patients with adjusted treatment, chemotherapy (30%) and immunotherapy (32%) were most frequently adjusted. Delay and discontinuation of treatment also mainly included chemotherapy and immunotherapy (see Figure).

Radiotherapy: Of all the treatment modalities, radiotherapy was associated with the lowest concerns about the risks of exacerbating the course of COVID – except where

irradiation of the lungs was concerned. Nonetheless, the impact on the risk–benefit balance of going ahead with treatment as normal had to be revised to take into account the risk of exposing patients to the virus by requiring them to travel to the treatment centre, and to be treated by staff and equipment potentially exposed to the virus. Restrictions in capacity were also a problem due to the time taken to clean the facilities between patients, the time taken for additional protective measures, and the need to minimise the number of staff in the unit at any one time.

Reassuringly, a fair level of evidence was already available on the impact of treatment interruptions and how best to manage them, as well as the relative effectiveness of delivering lower doses more frequently compared with higher doses spread across fewer treatment sessions – 'hypofractionation' – which seems to have been used widely across Europe during the pandemic.

Consultations and follow-up: Postponing or cancelling visits to hospitals that did not involve delivering treatments was one of the first and most widely implemented measures taken by European health systems. Many of these planned visits were replaced by remote consultations over the phone or internet. What was lost, in many cases, were opportunities for follow-up tests and imaging that could have given early signals of a recurrence or metastatic spread, or for monitoring toxicities that could avoid problems building up to a point where patients have to be taken off therapies they wished to continue.

The impact that will have in lost lives and lost life-years could – and arguably should – be modelled in the same way that has been done with delayed diagnosis of primaries.

Yet the shift towards greater use of telephone and internet consultations was not always a bad thing in the eyes of both practitioners and patients. Discussions about the pros and cons of greater use of digital communications between doctors and patients have been going on for more than a decade. The pandemic has acted as a catalyst that propelled a major shift towards remote forms of communication almost overnight.

Responses to the *Cancer World* survey (bit.ly/CW-COVID-survey) indicate that more than four in ten practitioners are conducting 'a few more' patient consultations over the internet or by phone, with a slightly larger number reporting 'a lot more'. Only just over one in ten said their mode of communications with patients had not changed. Surgical oncologists and oncology nurses were slightly less likely to report increased communication by phone or internet, but the trend was clear for all oncology professionals and almost all countries.

This communication change is likely to be one of the lasting legacies of the impact of the pandemic on oncology practice. While remote conversations work better for some patients than others, and are entirely inappropriate and unhelpful for some communications and discussions, they do seem to have worked well for both patients and medical professionals in many instances.

What worked well? What can we do better?

The spring and summer of 2020 put immense demands on oncology professionals, requiring them to be creative, collaborative and use all their medical knowledge and skills to do their best for their patients, with limited evidence, stretched capacity and in a climate of fear. The cancer community can be proud of the speed at which it responded to the challenge of generating evidence, through registries and research collaborations such as the COVID-19 Cancer Consortium Registry, the Thoracic Cancers International COVID-19 Collaboration (TERAVOLT), the UK Coronavirus Monitoring Project, COVIDSurg and many others. The evidence provided has been key in giving confidence to practitioners and patients alike to minimise the huge disruption to cancer care that was seen in the early period of the pandemic. It also provides vital ammunition for giving much greater priority to ensure timely diagnosis, care and follow-up of cancer patients and rapidly clearing the backlog.

But the pandemic is far from over; health services remain highly stretched, cancer patients remain in need of 'shielding' – some more than others; as of the end of September 2020, the pandemic seems to be resurgent across most of Europe; the possibility of a vaccine or improved treatment and care of COVID patients becoming available anytime soon remains uncertain at best. Oncologists and oncology services need to take stock of what has worked and what needs urgently to change.

Patient safety

Safety has to remain a big priority to protect patients from exposure to COVID and, importantly, to give patients confidence to engage with their diagnostic and care pathways. At the time of the *Cancer World* survey (early June 2020), more than one in four respondents said they had a COVID infection rate of between 1% and 5% in their departments, with a further one in ten reporting infection rates of between 5% and 10% (bit.ly/CW-COVID-survey).

On a rating scale of 1–10, respondents rated their confidence in the effectiveness of COVID screening for patients and staff at around 5. Confidence in access to adequate PPE, and in the measures taken to ensure visiting cancer patients were kept away from risks of COVID exposure was marginally higher, at a little over 6. More than three in four respondents were aware of protocols about how and where to treat cancer patients who were diagnosed with COVID.

Comments from respondents indicated that, even where good policies were in place, it was not always possible to carry them out. One Italian surgeon commented. "Please apply better the strategy!" A surgeon in the UK commented, "Here in Wales COVID 19 testing for staff seems very difficult and I have been refused testing three times. Patients for surgery tested after 14 days isolation – surgical teams NOT tested at all."

The difficulties accessing PPE made headlines across Europe during the early months, with the high worldwide demands pricing poorer health systems – such as in Albania – out of the market. While the situation has stabilised somewhat, problems clearly remain. An update on the situation in Germany provided in late August by one of the survey respondents indicated that, "It is better now, but the quality of the protective masks for example is often very poor. In some cases, protective equipment and disinfectants have been and are being stolen, or are only available to personnel in the infection areas. Sometimes everything is sold out or simply cannot be ordered. Smaller clinics and the outpatient sector have bigger problems, also because the prices for protective equipment have skyrocketed."

Going forward, the respondent would like to see more government support for provision of PPE, more testing of medical and nursing staff, and crucially better education of both staff and patients. "Precise information about risk management and necessary protective measures have a lasting effect on the behaviour of staff and patients. They can better understand processes and assess their own risk and implement the necessary self-protection and protection of others. Unnecessary fears and uncertainties can be avoided to ensure high-quality patient-oriented treatment."

Delays

Ending delays that are not supported by evidence, and addressing backlogs, will need to be an urgent priority moving forward. Responses to the *Cancer World* survey indicated serious concerns about delays to all elements of the pathway, but most particularly about cancer surgeries and above all diagnostic and follow-up tests. Focusing advocacy around addressing the multiple issues that led to the disastrous drop in new diagnoses and referrals, and delayed prompt access to curative treatment, makes sense in terms of the potential savings in life-years and health service expenditure.

There are concerns, however, that efforts to address the delays and backlogs in the preventive and curative setting could come at the expense of survivors, including those living with incurable cancers. Even those cancer services that made every effort to avoid delaying or interrupting cancer treatments were quick to cancel the great majority of hospital visits for follow-up checks. Concerns about delays in picking up recurrences and metastases were a frequent theme among respondents to the survey. Strong advocacy will be needed for this group of patients as well, to ensure that the delays and backlogs in follow-up visits do not continue – or even worsen – as systems try to redress the delays in the curative setting.

Protocols and pathways

Thanks to the prompt collaborative action in setting up cancer and COVID registries, new evidence will continue to emerge on risks and benefits of adapting standard pathways and protocols to the changing pandemic environment. Ensuring maximum participation in registries will be important. Rapidly spreading the evidence and emerging recommendations will also be essential.

Responses to the *Cancer World* survey indicate that one of the positive changes during the pandemic has been greater (internet-based) interactions and collaboration between cancer professionals, beyond discussions of individual cases at MDT meetings. "Webinars are very interesting to

communicate with colleagues of other hospitals," commented one respondent. Another talked about how greater communication had led to a better understanding of the different challenges faced by oncologists working in a general hospital environment compared with cancer centres. Many indicated that these sorts of interactions should continue. Making sure that happens will help ensure patients across Europe will benefit from emerging evidence as soon as possible.

As we have seen, however, evidence is not the only determinant of the care cancer patients can access. Asked to rate their confidence on whether changes to normal diagnostic treatment and care practices were being consistently implemented in the best interests of patients, the overall response was only 6 on a scale of 1–10.

Some of the more negative comments included, "Protocols during the pandemic were focused to overcome problems, not to improve quality of care," and "We are just 'washing our hands' with guidelines and making sure about 'legal implications', not aiming to provide the best for our patients." Advocating against deprioritising the interests of cancer patients during the pandemic will therefore be important going forward.

That said, many respondents also highlighted changes to pathways and protocols initiated during the pandemic that they felt improved the quality and efficiency of care and should be maintained moving forward. Attitudes differed markedly between disciplines. Almost 80% of both radiation and clinical oncologists were enthusiastic about some changes. Medical oncologists, oncology nurses and palliative care specialists were more evenly split, with between 50% and 55% indicating in favour. By contrast, only 40% of surgical oncologists indicated that they would want to continue with any of the protocol and pathway changes made during the pandemic.

Hypofractionation: Notable among the responses on protocols and pathways was the enthusiasm voiced by many clinical and radiation oncologists for using hypofractionated treatment schedules, which reduce the number of visits to radiotherapy facilities while maintaining an effective overall dose. That is an issue we can expect to read more about in the coming months.

A more critical approach: Other changes for the better that were mentioned by respondents highlighted the benefits of being obliged to question assumptions about the value of certain standard treatments in different patients. Examples of such comments include: "A more realistic assessment of risks and benefits of adjuvant or palliative chemotherapy"; "critical thinking about diagnostic and therapeutic procedures"; and "[better patient] awareness of what is really necessary for their pathways".

Examples given of decisions that received more critical scrutiny included the following: For patients with advanced cancer undergoing palliative treatments, are imaging exams really needed or are clinical assessments sufficient to continue or change therapies? Are complete blood counts really needed in all patients undergoing chemotherapy or is it sufficient for certain patients to contact their oncology team in case of new health problems? Are post-therapy follow-up exams really necessary, or is a phone call or a video conference sufficient? Is it reasonable to use therapies with fewer visits – e.g. once every 3 to 4 weeks – instead of more frequent treatment visits?

Communication with colleagues

Responses to the *Cancer World* survey indicate that greater use of videoconferencing and telemedicine was very widely welcomed, and we can expect to see a big change in the way communication is handled between members of MDTs and between professionals working in different parts of the system. Reported advantages include convenience, and also better discipline at preparing material in advance of discussions – something also mentioned in relation to communication with patients.

Other comments highlighted faster decision making: "We need to think about keeping the pace of decision making post COVID-19," and more-efficient record keeping, "Electronic therapeutic plans are now standard of care for most of our patients." Enthusiasm was also expressed for greater use of virtual communications for more general educational purposes, "All these new webinars should keep going, for more subjects."

Communication with patients

Attitudes towards greater use of remote communications with patients were more mixed. Among those who said they had increased their use of remote communication with patients, the satisfaction rate "in terms of communications with you and your patients e.g. breaking bad news and

discussing treatment options" was rated at just over 6 on a scale of 1–10. Among respondents overall, just over half indicated there were some changes to communications with patients during the pandemic that they would like to continue, going forward, with the remainder indicating they want a return to pre-pandemic ways of communicating.

Plus points were: fewer hospital visits were less disruptive for patients, ease of communication led to "more confidence between patients and doctors", oncologists could spend less time on routine conversations, giving them longer to spend on patients who needed more time. Negative points included limitations in the skills, familiarity and access to the right communications equipment (for doctors and patients), and the loss of important non-verbal communication – somewhat mitigated when using video links.

Almost all comments were qualified by stressing the importance of continuing with face-to-face consultations for specific conversations and specific patients.

The strongest comments, however, were about how pandemic restrictions are isolating patients in a way that is cruel and hampers effective communication.

The rule about no friends or family being allowed to accompany patients to hospital visits seems to have been implemented – for understandable reasons – across Europe. "This disturbs me highly on ethical grounds. Nobody should hear bad news about their health on their own," was one comment from Belgium. Another comment, from a Danish practitioner, argued that conversations aimed at helping patients reach the right decision for them, often require the

presence of family members or close friends, particularly when the news is not good. "Alone, most patients are quite vulnerable to these informations, and might not be able to catch all important details. Even more so when there are no treatments left to try, and the goal of the meeting is to plan for the few last weeks of life."

The respondent reported that her team tried using the phone on speaker, to enable family members to be present in conversations with patients, "but all non-verbal communication is lost and one cannot really know their reaction to some of the information. Plus, when there are conflicts, either between patients and us or internally in the family, it is not possible to ease this using body language. So in all, the 'interpretation' of the patient; how they feel, think, behave, the challenges they face and the support they have has been very much limited by the visitor's ban from outpatient clinics during COVID."

Protecting the caring aspect of cancer care

In some ways the pandemic seems to be forcing oncology services, in some areas, to become more efficient, quicker, more digital, more critical, and better at allocating time where it is most needed – all of which are to be welcomed. The big question posed by the Danish practitioner, however, is whether the human touch that is required to do the best for patients faced with difficult and distressing decisions can survive the current culture of social distancing.

"In my experience, the ethical standard of how we perform our work has been lowered, and my biggest fear is that this will become the new standard, as the pandemic will continue for many months and possibly years to come, and people already seem to have forgot how we did things before.

"I saw a nurse give a patient a hug yesterday. I haven't seen that in months, but it really shocked me that I even paid attention to it, as if it was some big issue. Six months ago I myself hugged patients without blinking, if that was what they needed. Now I hardly touch them. It affects the trust and loyalty that we have in our patient–doctor relationship. And though we try to compensate, the social distancing is as much psychological as it is physical, and I strongly believe it will lead to more conflicts and less understanding and trust in the years to come."

Maybe the biggest challenge for oncologists, as we move into the next stage of the pandemic, is to be aware of this danger. Just as webinars and online discussions about emerging evidence and best practice regarding protocols and pathways will be essential, so will sharing best practice regarding ways to combat 'psychological distancing' during, and after, the pandemic.

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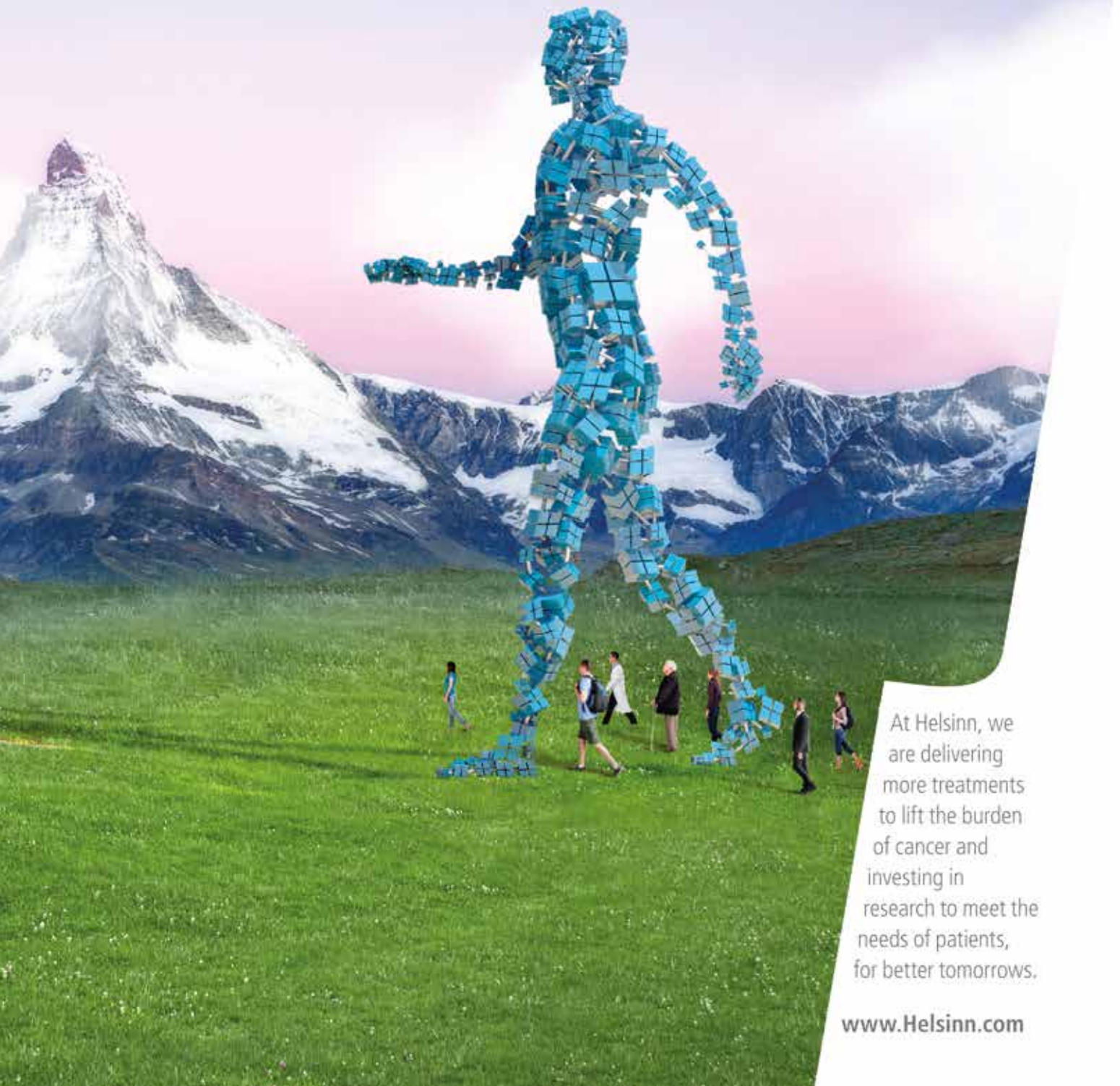

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Right drug, wrong patient: here's how we improve our targeting

Most of the revolutionary techniques now used to investigate cancers, their development and response to treatments were already 'old news' by the time **Balkees Abderrahman** entered cancer research. Currently a Living Legend Fellow of Cancer Research at the MD Anderson Cancer Center, and honoured by Forbes magazine 30 Under 30 as a leading young scientist, **Abderrahman** presents her perspective on why these techniques have not yet delivered on the promise of the right drug for the right patient, and how to make faster progress.

When it comes to precision and personalised medicine (PPM), clinical practice in oncology takes pride in developing and administering treatments that selectively target components of tumour cells. But, PPM is a model that also takes into account the inherent variability of patients' genetic, environmental and lifestyle factors, to identify which treatments would be most effective for which patient population. PPM does not consist merely of the selective targeting of tumour cells' components, but also that of patient populations.

One of the available tools of PPM that can facilitate this tumour-and-patient-selective targeting is 'companion diagnostics' – these are molecular assays that

measure the levels of genes, mutations, and proteins. However, when it comes to delivering new treatments to its suited patient populations, too few treatments coming on to the market leverage tools as companion diagnostics to allow for a 'lock and key model'. This accounts, in large part, for the failure of clinical practice in oncology to live up to early promises surrounding PPM.

Take chemotherapy, which remains the standard of care for many cancers. Traditionally seen as the antithesis of precision medicine, as it targets all rapidly dividing cells, its contribution to overall survival in the United States was calculated in a 2004 paper (Morgan G et al. *Clin Oncol* 2004) to be only 2.1%, due to limited specificity. Gene expression tests are now available that can avoid giving unnecessary chemotherapy to the majority of women with the most common form of breast cancer (i.e., hormone receptor-positive, HER 2-negative, and axillary lymph node-negative). While access to the tests remains patchy, and efforts to develop similar tests for other cancers are proving a challenge, the breast cancer gene expression tests offer an example of how PPM, when delivered to its suited patient population, can embody the Hippocratic Oath that all doctors must take before they practice medicine: first, do no harm.

The hope was that genome-driven therapies that target specific mutations would be much more effective because of their greater specificity in targeting tumour cells. But recent studies, such as the one by Marquart et al (Marquart J et al. *JAMA Oncol* 2018), indicate that as few as 5% of cancer patients in the US stand to benefit from these types of therapy.

So far, the story is not so different with immunotherapy. The treatment still lacks the tools to identify which patients will benefit, and which ones will suffer the adverse effects. PD-L1 expression in the tumour microenvironment is currently the standard and most widely-used biomarker to predict response, but it suffers several limitations.

Firstly, sampling a certain tumour site or at a certain time point might not reflect the state of the PD-1 or PD-L1 axis, because PD-L1 expression can be transient, with intrapatient and intratumour heterogeneity. Secondly, there is a poor uniformity in the immunohistochemistry antibodies used to test for PD-L1 as well as in the thresholds used to indicate PD-L1 positivity. Thirdly, PD-L1 immunohistochemistry does not take into account the influence of non-active immune cells at the level of tumour microenvironment, or concurrent suppressive immune pathways on anti-PD-1 or anti-PD-L1 therapy response.

Gay and Prasad's findings that only around 8% of all US cancer patients would benefit from immunotherapy should therefore come as little surprise (Gay N and Prasad V *STAT News,* March 8 2017).

Looking across all classes of cancer drugs, one 2001 study concluded that any class of cancer drugs is only effective in roughly 25% of patients (Spear BB et al. *Trends Mol Med* 2001). Although the following two decades have yielded a stream of targeted PPM oncology treatments, the translation of PPM into a patient population-targeted hit rate fell short of the tremendous technological advances seen in molecular biology. As a result, the vast majority of cancer patients still end up receiving ineffective and expensive treatments while suffering unnecessary adverse effects.

The scientific challenge

Developing PPM treatments for a disease as heterogeneous as cancer is certainly daunting, as there are more than 100 types, some of which have molecular subtypes.

One of the conduits to overcome this challenge is identifying biomarkers – these are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, and pharmacologic responses to a therapeutic intervention. Overall, they include pharmacogenomic, pharmacological, metabolomic, proteomic, toxicological and imaging indicators.

Early, predictive, non-invasive biomarkers enable drug developers to examine in some detail the efficacy and safety of an experimental drug in different settings, and make it possible for researchers and clinicians to select patients who would benefit the most.

But, finding effective biomarkers has been a challenge, not least because the expression of biomarkers can vary in the same tumour according to its location or stage, and also over time.

Boosting efforts to research and develop tools to assess the efficacy and safety of experimental drugs, including outlining the desired characteristics of biomarkers, is a central focus of the Innovative Medicines Initiative (IMI) – the world's largest public–private partnership, which was launched by the EU ten years ago, in an effort to accelerate

the development of new therapies in areas of unmet need.

With more than €5 billion in funding over the period 2008–2024, the IMI has made important progress, not least in facilitating collaborations between different competing global companies, small and medium-sized enterprises, and academia, while improving access to research infrastructure. Yet, such substantial efforts failed to act as the potent catalyst in translating PPM's mission of developing new specific drugs and delivering their benefit to suitable and wider groups of patients in Europe.

Does the frustrating pace of PPM progress so far in clinical practice in oncology indicate that we need to improve how we go about it, or that the early promises of PPM are unlikely ever to work well in a disease as complex as cancer?

Rethinking biomarkers

One developing line of thought that supports the more optimistic view, suggests that efforts so far have been held back by an erroneous assumption that predicting which patients will benefit or suffer harm when exposed to a given medical intervention, can be done by a single biomarker.

The suggestion is that 'combinatorial biomarkers' can be superior. For example, in addition to PD-L1 expression, there are other promising candidates for predictive biomarkers in immunotherapy. These include: tumour mutation burden (TMB), imaging biomarkers, peripheral blood T cells, T-cell receptor clonality, tumour-infiltrating lymphocytes (which might be an indicator of prognosis as well as predictive of response to immunotherapy), immune gene signatures, T-cell-inflamed gene expression profile (GEP), and description of the microbiome. A 2018 study (Cristescu R et al. *Science* 2018) showed that tumour mutation burden and a gene expression profile signature provided a predictive value for clinical response in patients treated on four KEYNOTE trials – KEYNOTE-012, -028 (Ott PA et al. *JCO* 2019), -001, and -006 (Ribas A et al. *Cancer Res* 2019).

Another area where a 'biomarker consortium' may become important is in the early detection of certain cancers, through the detection and analysis of volatile organic compounds (VOCs) in exhaled breath. Several trials are underway to identify and profile such VOCs.

Integrating new tools

Another emerging line of thought is that we need to incorporate new tools for PPM, other than biomarkers. One example is mass regulator proteins (MRs) – these are a few conductor proteins that orchestrate the largest networks of other proteins, dictate stability of cancer states, and drive cancer growth.

New research is demonstrating that, despite the heterogeneous cancer-triggering genetic and epigenetic alterations, the programme of gene expression – with its related protein activity that sustains a tumour for a given cancer type – is almost identical from one patient to another, and represents a real-time window into cancer activity. This makes it a very precise and valuable therapeutic target against cancer.

For example, in brain cancer (glioblastoma), three mass regulator proteins were shown to start and maintain cancer growth (Tome-Garcia J et al. *Nature Commun* 2018). This opens up important targets for PPM in treating the most aggressive form of brain cancer.

The discovery of mass regulator proteins adds a new tool for PPM, by shaking the tree for proteins – not mutations – to take centre stage for therapeutic targeting in oncology. It is also exposing the limitations of the long-standing belief that cancer is mainly driven by genetic mutations.

Shifting focus to early detection and precision prevention

Even if we become much better at developing and practising PPM in oncology, there is currently little evidence to indicate that it will offer the level of cure, long-term disease control, or enhanced quality of life that is desired in advanced cancers – at least in the case of solid tumours.

This means we need to focus more on strategies for primary prevention to prevent the disease before it happens, and secondary prevention aimed at early detection and, by this, minimising cancer spread and recurrence among patients. This sets the intent to cure cancer rather than just prolonging survival for weeks, months, or years.

Precision secondary prevention can constitute a valuable area in PPM. The use of the selective oestrogen receptor modulators tamoxifen and raloxifene has significantly prevented oestrogen-receptor-positive breast cancers; the use of the epidermal growth factor receptor inhibitor erlotinib has prevented some head and neck cancers, and the development of vaccines that can prime the immune

system to prevent cancer by targeting tumour-associated antigens, such as vaccines against hepatitis B virus, human papillomavirus, and mucin 1, has prevented hepatocellular cancer, cervical cancer, and some colorectal cancers, respectively.

One study estimated the US national annual treatment cost-savings from early cancer diagnosis of breast, lung, prostate, and colorectal cancers, and melanoma, to be in 11 digits (i.e., tens of thousands of millions of dollars) for the year 2017 (Kakushadze Z et al. *Data* 2017). Another UK-based study estimated that the cost of treating colon, rectal, ovarian and lung cancers at stage I is around 27%, 37%, 35% and 61% of the cost of treating the respective cancers at stage IV (cancerresearchuk.org/sites/default/files/saving_lives_averting_costs.pdf).

Getting PPM right: the three elements

Gathering data

Making PPM work well for large numbers of cancer patients involves first of all acquiring PPM data using various 'omics techniques (transcriptomics, genomics, proteomics, metabolomics, etc). This enables investigators to build up a picture of the biology of the disease – how it behaves in different hosts, and in response to different interventions. Getting this right is essential for developing experimental drugs, and guiding the trial design.

Developing interventions

Then, there's the question of developing the treatments themselves, which could take the form of monoclonal antibodies (to treat cancer), vaccines (to prevent, and in some cases treat, cancer), organoids (to model cancer biology, and examine cancer drugs' sensitivity and toxicity), and CAR T-cells (to treat cancer). This should be happening hand in hand with drafting regulations to facilitate an evidence-based assessment of the efficacy and safety of such novel drugs by the regulatory authorities. Regulators should be much stricter in requiring drug developers to integrate predictive and prognostic biomarkers into their workflow.

A 2019 analysis of oncology drug approvals awarded by the European Medicines Agency between 2014 and 2016, showed that around three in four of the randomised controlled trials that led to new drug approvals, measured indirect (surrogate) measures of clinical benefit, which do not necessarily predict survival or quality of life, while overall survival was a primary endpoint in only around one in four clinical trials (Naci H et al. *BMJ* 2019). If the exploratory work with biomarkers and companion diagnostics had been done more thoroughly, many of these trials could arguably have focused much more effectively on the suited patient populations, with clinically meaningful benefits in terms of survival and quality of life as the endpoint.

Addressing socioeconomic implications

Making that happen requires the third element, which involves addressing the socioeconomic implications of PPM. This could include, for instance, making pharmaceutical companies take on much more of the economic risk, when a drug they trialled in an imprecise test patient population eventually does not benefit many of the real-world patient populations. It also requires addressing ethical considerations to ensure, for instance, that PPM data can be shared effectively while protecting patient privacy.

The discovery of mass regulator proteins exposes the limitations of the belief that cancer is mainly driven by genetic mutations

In short, there is great hope regarding what PPM can achieve in oncology. Realising that hope will require many changes in how we go about developing and using PPM treatments. Key among them will be:

- optimising the design of clinical trials with the incorporation of PPM tools (i.e., biomarkers, etc),
- exerting quality control over the regulations of new drug approvals,
- developing combinatorial biomarkers that address the complex interactions between the host, tumour, and tumour microenvironment,
- developing new PPM tools (from optimisation of assays to clinical validations, to assessments of clinical utility), and
- shifting the focus of research and development to early detection and prevention, remain areas of improvement; to fulfil the promise of PPM and benefit far more patients.

Prognostic biomarkers

Could they help doctors, patients and families to better navigate the end of life?

By Janet Fricker

"We had to explain that the reason she had broken her hip was because she was getting weaker and essentially dying… At that stage, knowing whether Mum had days or months left would have been an important factor."

Helen Waddell, talking about her mother Liz Skinsley

"I wish we'd had the opportunity to plan our lives about the fact we were dealing with the last few years of our son's life. As a family we'd have gone on more holidays. We've lots of good memories, but also bad ones, and the bad ones are of missed opportunities. It leaves you with regrets about the things you thought you had plenty of time to say and do, but never managed."

Tony Bonser, talking about his son Neil

While the two quotes above talk about very different experiences, the point they make is the same: having a clear idea about how long a loved one will live is essential to making the most out of their remaining days, weeks or years.

Yet data from the UK's National Audit of Care at the End of Life (NACEL) reveal that around half of patients are recognised to be

dying less than one and a half days before they actually die.

Knowing a person is nearing death provides the ultimate in personalised medicine. "If we can recognise the dying process we have a real chance to make that experience as good as it can possibly be, and give patients the highest quality of care at the end of life," says Seamus Coyle, a palliative care consultant from the Clatterbridge Cancer Centre, Liverpool.

The predicament facing clinical staff – not least oncologists – is that prognostication, predicting when a patient is likely to die, is an inexact science with little in the way of an evidence base. "Prognostication in advanced cancer is currently an unmet need," says Barry Laird, a Reader in Palliative Medicine at the University of Edinburgh. "It represents a crude art form largely based on clinicians' intuition/experiences, which are often optimistic, informal and subjective."

Benefits of prognostication

Prognostication brings multiple benefits throughout the cancer journey, not least providing clarity to both clinical and patient decision making. It offers the opportunity to focus on the quality of the patient's remaining days, and put a stop to the pursuit of inappropriate aggressive therapies. In the absence of good prognostic information, the healthcare machine continues its relentless pursuit of cure at all costs, with the full gamut of tests, investigations and treatments. A systemic review of 38 international studies, evaluating 1.2 million patients in total, demonstrated non-beneficial administration of drugs (including antibiotics, cardiovascular, digestive and endocrine treatments) occurred on average in 33–38% of dying patients (Cardona-Morrell M et al. *Int J Qual Health Care* 2016). "These behaviors have repercussions… on the capacity and financial sustainability of health services, and perpetuate the unrealistic high social expectation of survival at all costs, but also more importantly reflect a disregard for human dignity and quality end of life," wrote the study author Magnolia Cardona, from Bond University Australia, and colleagues.

Recognition that a person is entering their last year of life enables advance care planning to be implemented, allowing discussions about the personal goals and wishes of the dying person. "Missing these conversations represents a major lost opportunity. Without them there's no way to ensure end of life care aligns with what matters most to the patient," says Stephanie Harman, a palliative care doctor at Stanford Health Care, California.

Providing good quality palliative care is an important component of advance care planning, which perversely enables patients to live longer. A study of patients newly diagnosed with metastatic non-small-cell lung cancer, by Jennifer Temel from Harvard Medical School, found cancer patients randomised to receive early palliative care integrated with standard oncology care lived on average for two months longer than those receiving standard oncology care, and furthermore they enjoyed better quality of life and fewer depressive episodes (Temel JS et al. *N Engl J Med* 2010).

It offers the opportunity to focus on the quality of the patient's remaining days, and put a stop to the pursuit of inappropriate aggressive therapies

Prognostic information helps clinicians to consider palliative care treatment decisions, such as whether to offer radiotherapy. "We need prognostic information to weigh up whether patients will live long enough to benefit against the disturbance of having treatments in their last few weeks of life," says Laird.

Knowing death is imminent allows for timely referral to hospices, which are usually unable to offer care beyond a few weeks. When death is thought to be just a few days away, the dying can be prescribed drugs to manage symptoms such as noisy respiratory secretions and terminal restlessness, which can distress patients and their families.

Knowing that time is short can be especially valuable for families, allowing them to organise their lives to be with dying relatives. "As a family it came as a real shock when a doctor told us my father was unlikely to survive the week. Had I known that he was terminal I would have structured my life differently and

moved back to be with him," says Muhammad Ahmad, who is now working at a US assistive intelligence company on an algorithm to predict when people are likely to die.

Why are patients given so little information?

Undoubtedly, one of the issues behind lack of prognostic awareness is that many cancer patients have no comprehension of their prospects. A study of patients with newly diagnosed metastatic stage IV lung and colorectal cancers found that 69% and 81% respectively believed the palliative chemotherapy they received was intended to cure them (Weeks JC et al. *N Engl J Med* 2012). This finding is supported by a study of patients with advanced cancer who oncologists expected to die within six months, which showed that only 5% of the patients had a completely accurate understanding of their illness and 38% reported that they had never discussed life expectancy with medical staff (Epstein A et al. *JCO* 2016).

One explanation for lack of understanding may be the absence of explicit prognostic communications between patients and healthcare staff. A study of audio recorded 'bad news encounters' between oncologists and patients, by Toby Campbell from the University of Colorado, found 'scan-talk' – offering news of a prognostic nature – occupied less than 10% of the entire conversations, while 'treatment-talk' occupied 50% (Singh S et al. *J Oncol Pract* 2017). The authors comment on a 'natural collusion' between patients and doctors, writing "We observed immediate transition to treatment-talk during the disclosures of bad news, which potentially contributes to patients' misinterpretation of their prognosis and stifles any further discussions surrounding prognosis."

'Scan-talk' – offering news of a prognostic nature – occupied less than 10% of the entire conversations, while 'treatment-talk' occupied 50%

Doctors may shy away from candid discussions due to sensitivities around being the bearer of bad news. A study of people watching videos of patient encounters showed that doctors delivering optimistic messages were perceived as more compassionate and trustworthy than those delivering less optimistic messages (Tanco K et al *JAMA Oncol* 2015).

There is also the question of how accurate doctors are at prognostication. A study co-authored by Nicholas Christakis, from the University of Yale, reviewed survival estimates made by 343 doctors for 468 terminally ill patients. The study found that, on average, doctors predicted that patients would live 5.3 times longer than they actually did (Christakis N and Lamont E *BMJ* 2000). In his 2001 book, 'Death Foretold', Christakis describes 'the ritualisation of optimism', arguing that the challenge of prognosis causes most doctors to shirk difficult conversations around end-of-life planning and instead hope for the best. "Clinicians go into this business because they're optimistic about the care they can deliver, which makes them somewhat biased," says palliative care specialist Stephanie Harman.

Current prognostic tools are very inaccurate

Perhaps the overriding reason for lack of information, hindering the efforts of even the most assiduous oncologists and palliative care doctors, is that the current prognostic tools for predicting death are hugely inaccurate.

Around the time of cancer diagnosis, prognostication primarily relies on staging the extent of the disease and grading the appearance of cancerous cells. But as Paddy Stone, Professor of Palliative and End of Life Care at University College London, points out, "While this information helps make treatment decisions, simply knowing the patient has stage IV disease won't necessarily distinguish those people with life expectancies of days from those who might still survive years."

Later in the cancer journey, measures such as the Karnofsky Performance scale (providing a score of 0 to 100) and Eastern Cooperative Oncology Group (ECOG) Performance status (providing a score of 0 to 5), are used to help prognosticate. These summarise the ability of patients to perform daily activities and, although not initially devised as

prognostic tools, have been shown to correlate with survival. "Such scales are subjective," says Laird. "Unless you watch the patient every day, they're little better than guesstimates. Patients often dress up to visit the doctor and give the impression they're functioning much better than they really are."

An alternative approach for identifying people who might benefit from palliative care is the 'surprise question', with clinicians asking themselves "Would I be surprised if this patient were to die in the next six to 12 months?" The binary 'yes' or 'no' answer provides little indication of the actual length of time left. "Putting a timeframe on life expectancy is a bit like predicting the weather," says Stone. "Short term weather forecasts over the next three to 14 days can be really accurate, but it's not so good for considering events over the next three months to a year."

Despite all this, it is the intuition of clinical staff that is still considered gold standard approach. "There have been papers suggesting doctors do better, and papers suggesting nurses do better. What seems true is the combined efforts of multidisciplinary teams are best," says Stone.

Could prognostic biomarkers help?

Realising the inherent limitations of prognostic tools, a number of investigators are looking to devise new methods. Barry Laird believes documenting inflammatory status offers the potential to deliver greater accuracy. For this he uses the modified Glasgow Prognostic Score (mGPS), where C-reactive protein (CRP) provides a positive marker of systemic inflammation and albumin a negative marker. For the scale, Laird explains, if CRP and albumin levels are normal, the patient has a score of 0; if CRP is elevated but albumin normal, the score is 1; and if CRP is elevated and albumin low, the score is 2.

In a study, Laird showed that three-month survival for patients with advanced cancer varied from 82% for those with mGPS 0 to 39% for those with mGPS 2 (Laird BJ *Clin Cancer Res* 2013). Laird believes even better prognostic results can be obtained by combining mGPS with ECOG scores. In a recent study he showed that if patients have an mGPS of 0 and an ECOG score that is functionally good, 88% will be alive at three months, whereas if their mGPS is 2 and ECOG 4, only 10% would be alive at three months.

"Such scales are subjective… Unless you watch the patient every day, they're little better than guesstimates"

The GPS also reflects the degree of tumour-related cachexia; at the June 2020 Sharing Prognosis in Cancer Care (SPCC) Task Force on Cachexia, Jann Arends from the University of Freiburg suggested that the GPS might be used as a screen for pre-cachexia in cancer patients. Since cachexia accounts for 20–30% of cancer deaths, developing the condition undoubtedly represents a poor prognostic sign.

Paddy Stone developed the Prognosis in Palliative care Score (PiPS) to allow a greater number of prognostic factors to be taken into consideration. From a systematic literature review he identified 50 candidate variables reported to predict survival in advanced cancer. More than 1,000 terminal cancer patients then had these variables measured shortly after referral to palliative care services, with a multivariate data analysis undertaken to see which related to survival when patients were followed up until most died.

The analysis identified 11 core variables (pulse rate, general health status, mental test scores, performance status, anorexia, metastatic disease, liver metastases, C-reactive protein, white blood count, platelet count and urea) predicting both two-week and two-month survivals.

From this, Stone went on to develop two different prognostic models, one without blood results (PiPS-A) and one with blood results (PiPS-B). In the original study, he and co-authors showed both models were at least as good as multi-professional clinical estimates of survival, and that PiPS-B was significantly better than either a doctor's or a nurse's prediction, but no better than a multi-professional estimate (Gwilliam B et al *BMJ* 2011). The results of a confirmatory study involving another sample of more than 1,000 advanced cancer patients are expected soon.

To identify patients on general medical wards who would benefit from advance care planning, Stephanie Harman has taken the

concept of mathematical modelling one step further, using machine learning. Perhaps best known for powering Google suggestions in internet searches, machine learning is the process by which computers train themselves to identify subtle patterns in data. Harman and colleagues, from Stanford Health Care, collected de-identified data from more than 10,000 general medical patients at the same institution, which was used as a 'training set' to identify common features among patients who subsequently died over the next 12 months.

In a pilot study (currently on hold due to COVID-19) the team plan to use computers to systematically compare new patient data with the 'training set', to flag up high-risk patients. "It's a way to prompt clinicians when they've got really busy work flows to stop and find the time for advance care planning conversations," says Harman.

One limitation of the Stanford approach is that the 'black box' nature of the system makes it difficult to tell how the model derived its conclusions.

KenSci, an assistive intelligence company that came out of the University of Washington, is developing interpretable models, where the platform specifies the reason why the end of life prediction was made. "Since models are wrong 10% of the time, having an explanation gives clinicians far greater confidence in findings," says Muhammad Ahmad, principal data science researcher at KenSci.

Seamus Coyle is looking for chemical signatures in the urine of terminally ill patients that may signify they are in the last few days of life. He takes inspiration from the story of Oscar, a therapy cat in a Rhode Island nursing home, who predicted the impending death of more than 100 terminally ill patients by curling up to sleep next to them (Dosa D *N Engl J Med* 2007). One theory is that Oscar used his acute sense of smell to detect volatile organic compounds resulting from patient's organs shutting down.

Coyle's research is using mass spectrometry to measure around 100 different chemicals, to define a characteristic 'fingerprint' signifying death is imminent. In a preliminary study, Coyle compared the chemical signatures of 30 lung cancer patients in the last week of life, and 30 in the second-to-last week of life, with 100 lung cancer patients whose conditions were not terminal, leading to definition of a tentative signature Coyle plans to verify in future studies.

"Ultimately, we hope to be able to feed the chemical information into a computer programme to come up with a binary score (yes or no) of whether the patient is in the last few weeks of their life," he explains.

Lia van Zuylen, Professor of Palliative Cancer at Amsterdam UMC, is interested in identifying the last few days of life, using proteomics to look at protein changes in the urine and an under-the-tongue probe to identify impairments to the microcirculation (the capillaries responsible for the exchange of oxygen and nutrients between the vasculature and adjacent cells).

"Establishing the physiological process of dying would make doctors more aware of the existence of a dying phase, and help them to communicate better with their patients," says van Zuylen.

"We hope to be able to feed the chemical information into a computer to come up with a binary score of whether the patient is in the last few weeks of their life"

Talking honestly to a patient about their death is arguably one of the most difficult tasks undertaken by health care professionals. Few doubt that developing better prognostication will enhance dialogues, but for these conversations to be truly effective, greater emphasis will also need to be placed on interpersonal communication skills.

It is not enough for health professionals to tell patients they are nearing the end of life, they need to be sure that their patient fully comprehends what has been said to them.

As van Zuylen emphasises, healthcare staff have one chance to get it right. "Dying is a unique and irreversible experience that cannot be redone. It's important not only for patients, but also for family members.

The way a loved one dies leaves deep marks in memories that have repercussions for the rest of your life."

european cancer ORGANISATION

Matti Aapro, President,
European Cancer Organisation

From 1918 to 2020, the lessons of pandemics remain: health systems must be kept strong, and international health cooperation underpinned

"The new normal" and "unprecedented times" are phrases all of us will be familiar with hearing this year as the shock of COVID-19 continues to reverberate. And yet, in a broader historical view, pandemic infections have long been a 'normal' for our species. I write this not to in any way trivialise the whirlwind of damage being created by COVID-19 and reactions to its effects, but rather as a means of reassurance that we have been here before, come through the other side, and occasionally, put in practice vital lessons from the important learnings derived from the experience.

Without going to the times of the plague, I think, for example, of the cruel so-called 'Spanish Flu' of 1918, that callously tore through countries at the closing of the First World War, robbing the lives of an estimated 50 million persons worldwide and leaving enormous economic and social scars behind. Critical lessons were learned at this huge price, such as the need for strong and resilient health systems, and international vigilance and cooperation against public health threats.

This comes to mind as we anticipate the closing months of 2020 and what they might mean for European cooperation on cancer. One simplistic approach might be a knee jerk response to deprioritise all EU initiatives not considered directly relevant to combatting COVID-19 and its effects, and the rebuilding of our health and economic systems. The other, more visionary and long-looking view, is to grasp that, as with any event of such enormous proportions, be it health emergency, financial crash, war or other, seeking a quick return to the old is illusory. Things neither can, nor should, go back to the way they were.

So with Europe, the EU and health. After COVID-19, who really, in honesty, can imagine that pan-European health cooperation will return to be the minor part, the secondary consideration, of inter-governmental collaboration? To do so would be an insult to all those who have suffered so much as a result of this health crisis, which knows no artificial limits.

That is why, in May 2020, when EU Commissioner for Health and Food Safety Stella Kyriakides announced to members of the European Cancer Organisation that she was pursuing the establishment of a new €9.4 billion European Health Funding mechanism, we responded with delight. A politician who understood the moment, and the response that we owe to future generations.

It is also why it was so crushing to learn that the EU Council of Ministers subsequently determined to cut the proposal to a severely reduced €1.7 billion.

This is the side struggle that takes place at our present time in respect of COVID-19. What world will we build out of the other side of the crisis? One of continued small thinking on health cooperation, or one that extracts positive change from the grim experiences endured by all?

As we work with the European Parliament, European Commission and Government representatives to continue conveying the opportunities that exist from the new EU Beating Cancer Plan, Cancer Mission and Pharmaceutical Strategy, in four months we will have a better sense of which side has gained ground in that battle of ideas: the advocates for the old world, or for the new world.

The cancer community cannot be bystanders in this contest. Like COVID-19, cancer knows no borders. The global battle against disease and poor health should not either. It is the borders of some political leaders' imaginations for the post COVID-19 world that must be opened now.

Raed Al Dieri: Taking pathology from bit part to key player on the European oncology scene

With precision medicine, pathology has moved out of the labs and into the heart of clinical decision making. But the discipline has struggled to make its voice heard at the level of professional oncology societies and policy making. Raed Al Dieri of the European Society of Pathology talked to **Simon Crompton** about his plans to move pathology to centre stage.

The man steering the organisation dubbed "the leading force in European pathology" is not one to dwell on the negative. Raed Al Dieri, Director General of the European Society of Pathology (ESP), is an internationalist but also a proud Syrian. He confesses to finding it hard when people ask him about how he feels about the devastation ten years of war has wreaked on his homeland.

He finds it difficult that the only image most people have of his country – one of the most ancient and influential civilisations on earth – is one of destruction and suffering. "You're talking about a country with thousands of years of history, strongly rooted in every field of education," he says. "People don't know about our high levels of education." And while he is extremely sad about what has happened, he expresses confidence that situation is going in the right direction, "I feel optimistic that in the end everything will be corrected."

So too in pathology, Al Dieri is happy to play the long game – measuring the timeframe for meeting his goals in terms of decades rather than years. "We are getting there," he says repeatedly, as we talk about the challenges faced by the profession: the status of pathology in the multidisciplinary team, issues of quality control, understaffing of pathology services, training and updating all levels of the profession to meet the increasing demand for pathology expertise in the face of rapidly evolving science and technology.

The fact that there are challenges to be faced is a mark of how much pathology in cancer has developed over recent decades. Before 1970, cancer pathology was based almost entirely on observing the morphology of cancer tissue under a microscope. With the development of immunohistochemistry, individual cell components could be identified, opening up the way to biological tissue characterisation and the identification of important biomarkers for diagnosis, prognosis and predicted response to therapy.

"The role of the pathologist is no longer simply in diagnosis, but in prediction and prognosis"

In the 1990s and 2000s, pathologists became able to measure oestrogen receptors and HER2 status. Then as targeted therapies started to become available, molecular markers, which had previously been used for diagnosis and prognosis, became specific targets for interventions. As the age of precision medicine has developed further in the molecular era, the information provided by pathologists has become more directly important to patient treatment, capable

of predicting the most suitable drugs and outcomes.

"Cancer as a field is being very much progressed by the research and understanding being provided by pathologists," he says. "The role of the pathologist is no longer simply in diagnosis, but in prediction and prognosis."

But this game-changing evolution of pathology has not always been reflected in an evolution in working practices.

A place on the team

Ten years ago, talking to *Cancer World*, influential Italian pathologist Giuseppe Viale warned about worrying variations of pathology practice and standards across countries and across Europe. Too many pathologists, he said, were not involved in multidisciplinary teams (MDTs), effectively isolated from structures that could now drive work searching for specific targets and treatment options and help maintain and improve quality.

This is now changing significantly, says Al Dieri. Since becoming Director General of the European Society of Pathology three years ago, he has made it a priority to combat professional isolation, improve standards and nurture understanding, by raising the profile of pathology with all health professions. He has been an active participant at international cancer conferences and policy meetings, keen for pathology to be understood as a key cancer discipline alongside surgery, medical oncology, radiotherapy and other medical disciplines.

"I feel we need to be more engaged with our colleagues at other medical societies," he says. "Personally, I feel that pathologists are no longer at the back-stage, but we need to be more visible."

This applies also to the profession's involvement in MDTs. Yes, in some European countries it is harder to break down old professional hierarchies and structures. But generally, he says, there is now no choice. It is "only a matter of time" before the outliers fall into line. "Generally disciplines like oncologists and radiologists understand very well the importance of engaging pathologists if you are going to select the right treatment."

A place in cancer research

Ensuring the full pathology contribution is recognised within MDTs is intricately linked with collaborating with other professionals at all levels. Involvement

with other professions in research, for example, is key not only to joint working for its own sake, but to raising standards and improving patient care.

Here too, Al Dieri has a vision. "I would like to see pathologists more engaged in clinical trials," he says. Three years ago, under his tenure, ESP established a new pathology research fellowship programme in collaboration with the European Organisation for Research and Treatment of Cancer (EORTC). It recognises the central role of pathologists in clinical trials in the era of precision medicine and especially in the field of medical oncology.

Pathologists, he points out, are the custodians of the annotated biological samples used in biomarker-driven studies, ensuring all prerequisites for reliable molecular testing and reporting are fulfilled. So, in the era of precision medicine, involvement in clinical trials is intricately linked with the growing importance of quality control.

"I would like us to be more and more active in the field of quality control. At ESP we already provide quality assurance programmes in certain areas. I would like to extend this, with more laboratories participating not only in Europe but across the globe. Because, in the end, the organisation's vision is excellence in pathology for optimal patient care. What does patient care mean? It means the appropriate diagnostic tools interpreted very well in order to have the right diagnosis and the right treatment for our patients. I see challenges ahead, but I'm sure we'll be able to find our way through it and achieve our goals."

The European Society of Pathology

*The **European Society of Pathology**, founded in 1964, aims to promote high quality diagnosis, practice, research and education, working through its congresses, journal, fellowship programmes, courses and quality assurance projects. It interacts with national pathology societies across Europe and has more than 20 working groups in specialist areas of pathology.*

Reaching out

Before his appointment as Director General in 2017, Al Dieri spent five years as the organisation's scientific director. His background, however, is in pharmacology not pathology – which he sees as a strength when it comes to reaching out to clinicians and their organisations.

He brings to the job the experience of a long and distinguished research career, specialising in thrombosis and haemostasis, which took him deep into every area of laboratory diagnosis and into contact with every medical discipline. The understanding he gained about the mechanisms for diagnosis, prognosis and follow up, he says, helps him get messages across to medical colleagues. As he points out, there are few cancer specialists who will not have come across thrombotic complications.

"The multicultural and international collaborations I've been involved with have provided me with a strong platform for reaching out"

The son of a vice director of a pharmaceutical company, from an early age Al Dieri felt "close to medications, the effect, how you have to handle issues," and he studied pharmacy at Bachelor's and Master's level at Damascus University, before (on the basis of outstanding results) being appointed a teaching assistant at the university faculty of pharmacy. He was, he says, lucky to be educated at such a high-level university and academic hospital.

His whole family had a medical bent (his sister is an ophthalmologist) and was always outward-looking, regularly travelling and with many professional contacts and friends in Europe. So it didn't seem too large a leap for him to go to Maastricht University, in the Netherlands, to complete a doctorate in haemostasis and thrombosis in 1996.

"I was very motivated to pursue mode of action and mechanism of diseases as well as new medications," he says.

What followed was a productive research career during which he co-developed a new (and patented) method for measuring the coagulation system and the activity of anticoagulants. He then spent nearly ten years as Research Director of the Synapse Research Institute in Maastricht, supervising and conducting clinical and fundamental research.

This has stood him in good stead at the ESP – the critical thinking needed to head an organisation is the same, he says. "You need political and communication skills to lead an organisation, and I've also been able to bring what I learned in research and education to that. The multicultural and international collaborations I've been involved with have provided me with a strong platform for reaching out.

"It's about more than promoting a multidisciplinary approach," he adds. "You have to reach out to the European Union and medical societies to address common issues, as well as the issues we face as individual professions.

A service clinicians and patients can depend on

Given increasing recognition of the contribution pathology makes to cancer treatment, one of the key issues facing Al Dieri since his arrival in the hotseat has been how to meet demand – both for pathologists themselves, and for highly developed skills in the molecular techniques that make them so crucial to good cancer outcomes.

"There's no need for every pathologist to become a fully-fledged molecular pathologist, but they do need to fully understand the methodologies"

Al Dieri is adamant that only pathologists have the ability to both identify significant characteristics and changes through molecular testing and interpret them in a morphological context. But the developing technologies and the increasing number of biomarkers now identified does make this an increasingly specialist area.

"We have to work very hard to make it possible for the current and new pathologists to get the appropriate training," he says. "In Europe we are suffering from shortages of pathologists in general, and because precision medicine is now so important in cancer, we need to do something. ESP cannot really solve the problem itself. We need a European and international strategy and we need action at a national level as well."

A key starting point is a robust technological methodology that meets requirements set by pathologists and molecular biologists. The tricky part is implementing quality control on that methodology, once agreed.

"You need to minimise or eliminate mistakes, because these can lead to disaster for the patient. This is why ESP is taking serious steps, like other pathology organisations at a national and international level, to provide quality assessment programmes for diagnostic molecular testing. Pathologists need to be tested for proficiency, at least on an annual basis."

ESP is also providing postgraduate training programmes in molecular and histopathology. Al Dieri is all too aware that some countries are more able than others to address the challenges nationally.

"I can envisage problems if countries cannot provide training for young pathologists to be able to cope with the new information as well as emerging technical issues," he says. There's no need for every pathologist to become a fully-fledged molecular pathologist, but they do need to fully understand the methodologies, so that they can select and test samples adequately and then incorporate their morphological analysis with the molecular analysis in the diagnostic report.

"Pathologists need to be engaged at every point of molecular testing: before, through and after. It is extremely important at the later stage when the resulting medication is prescribed to the patient. That is the vision. But it would take at least two decades to have this fully implemented, but on different levels, in different European countries."

Education has always been at the core of ESP's activity, and coincidentally the organisation was already developing more interactive e-learning programmes and platforms before COVID-19 hit and the world seemed to go online. Al Dieri, ever the internationalist, wants these programmes to be a global rather than a European resource: the organisation's membership extends to 100 countries. He feels passionately about continuous education.

"Young pathologists need to be continuously supported," he says. "It's not a matter of doing something once and then feeling you're done. At ESP we feel a responsibility to act more aggressively in providing continuous education programmes. You need to be challenged at every level. Undergraduates, post-graduates, even certified pathologists, all need to constantly update their knowledge."

"Undergraduates, post-graduates, even certified pathologists, all need to constantly update their knowledge"

Al Dieri lives in no doubt that there are hurdles to overcome: in cancer in particular, revolutionary technological changes and new concepts for treatment have brought the need for a seismic shift in mindset and structures. But, as he says, we are getting there. As we end our interview, he reflects on the situation in Syria, and his words reflect on his professional work too. "That's life. You have to live a certain amount of time with the challenges."


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The European Parliament in Brussels lit up in gold in support of Childhood Cancer Awareness Month!

The year 2020 is proving to be challenging as the world is confronted with an extraordinary global health emergency and everyone's attention is focused on one disease only: COVID-19. We must remember cancer has not gone away!

In this unprecedented year, CCI Europe (representing parents/patients), PanCare (a network of childhood cancer survivors and professionals working in this field) and SIOP Europe (paediatric cancer healthcare professionals and academia) joined forces in support of **Childhood Cancer Awareness Month** this September.

We extend our deep gratitude to Honourable Vice-President of the **European Parliament**, Ewa Kopacz, for championing the European Parliament endorsement of this September's **'Shine Gold'** Campaign. The lighting of the European Parliament building in Brussels (1-6 September) brings much needed visibility to the persistent burden of cancers affecting children and young people, and is an important signal that the youngest citizens will not be left behind. Our entire European childhood cancer community is delighted that this year's campaign has received such exceptional support.

Through the symbolic gesture of lighting the building in gold, the European Parliament is bringing it to the attention of all stakeholders and citizens that too many young lives are still lost to childhood cancer, but that the EU is well positioned to make transformational change possible.

This year's campaign aimed to reach out to a broad audience across Europe with accessible information on the stark reality of **childhood cancer – the number one cause of mortality in children** older than 1 year. The facts highlight the urgency:

- Every 15 minutes in Europe, a family receives the devastating news that their child has cancer.

- Over 6,000 children and young people are dying every year in Europe from childhood cancer. This equates to as many as 200 school buses.

- There are 35,000 new cases of childhood cancer in Europe each year. This equates to a football stadium at full capacity.

- Almost 500,000 long-term survivors of childhood cancer live in Europe today. This equates to the population of a large European city, such as Antwerp (Belgium), Lyon (France), or Lisbon (Portugal).

- There are up to 20% differences in survival of children with cancer amongst European regions.

- Ten times less public funding is allocated to childhood cancer research in Europe than in the US. Europe should strengthen its position as a leader in childhood cancer research globally. More funding is urgently needed for childhood cancer research.

Children and young people should be able to benefit from faster and more efficient development of affordable innovative medicines. The cure rate must improve – indeed we must cure more and cure better, as detailed in our **Manifesto for the paediatric oncology and haematology community**.

Pamela Kearns (SIOP Europe President): *"Cancer hasn't stopped because of the Coronavirus. The sad reality is that COVID-19 has in fact had a devastating impact on research and clinical trials. The research of today produces the treatments of tomorrow, so it's really important to highlight the challenges that we are facing and urge all the various stakeholders to continue their work for a brighter future for children and adolescents with cancer."*

Samira Essiaf (SIOP Europe CEO): *"Together with a terrific team that is worth its weight in gold as well as our partners, we aim to make a difference across the EU and beyond for children and adolescents with cancer as well as for childhood cancer survivors. This year's September campaign was the first of its kind and we are determined to do more next year."*

We are also pleased that local Belgian media (newspapers, magazines and TV) have recognised the importance of this message and are featuring Childhood Cancer Awareness Month. These local media outlets so far include RTV, VRT, *Het Laatste Nieuws*, AVS Television, TV Bruzz, *Nieuwsblad, Gazet van Antwerpen, Knack,* and we are confident others will follow. Such positive reactions are promising, and we will continue to increase awareness of the needs of childhood cancer to enable a better future for these brave young people.

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Malignant

Insights into the process of metastasis and how we can stop it

In the majority of cancers it is the metastases and not the primary tumour that prove fatal. **Adriana Albini** reviews steps in the malignant process and strategies to block it.

Why and how do cancer cells travel from their original site to seed new tumours elsewhere in the body, and what can be done to stop them? A series of presentations at the virtual June 2020 annual meeting of the American Association of Cancer Research (AACR) showcased some of the fascinating insights that are helping piece together the evidence.

Two scientists, Zena Werb and Josh Fidler, who helped open up this area of research long before it became the hot topic that it is today, passed away only weeks before the AACR congress. This review is dedicated to them.

Beginnings of a metastatic cell

As we now know, the seed of cancer is a single transformed cell, which begins to multiply and grow in an uncontrolled way. It may be dormant for a while, but then it wakes up and divides into daughter cells. Through further mutations the initial clone gives rise to other clones, as they evade the control mechanisms used by cells and by the body to guard against carcinogenic transformation, leading the initial tumour to become increasingly aggressive.

However, a malignant tumour will not be content to remain restricted

to the area where the tumour arose. Some of the crazed cancer cells will metastasise – a process by which they detach from the initial mass, and head to distant organs. The trip starts, and it has a precise destination – a colon cancer may send emissaries to the liver, while a prostate neoplasm will colonise the bones. Patricia S. Steeg, who gave the Women in Cancer Research Charlotte Friend Lectureship at the virtual AACR, has focussed her recent studies on breast cancer brain metastases. For many patients, this process spells the transition from a potentially curable to an incurable cancer, so understanding the metastatic process and developing ways to intervene to slow or halt it is a very important area of research.

The first step towards a cure for a metastasis is to get to know malignant cells better. But we also need to understand the role of the tumour 'microenvironment' – the apparently healthy tissues within which the tumour develops and which malignant cells hijack for their own ends to help them at all stages of their metastatic journey.

Leaving the primary tumour: drivers, obstacles and strategies

The search for a more satisfactory environment seems to be a key motivation driving 'restless' cancer cells to break free of the primary tumour and go in search of a hospitable place to colonise. One potential cause of dissatisfaction with their initial environment is the dwindling levels of oxygen available within the tumour mass as the cancer grows, which makes for a 'suffocating' (or 'hypoxic') environment. Is it surprising that cells should move in search of a 'breath of fresh air'? They relocate to a 'more comfortable apartment'. Defining the mechanism by which alterations in cellular oxygen lead to changes in the cells' gene expression won three researchers the 2019 Nobel Prize in Physiology or Medicine.

And yet cells do not circulate freely around the body. In order to move, they must continually cross the matrix, or barrier cells, such as endothelium or epithelium. Isaiah 'Josh' Fidler, who died in May 2020, was one of the most important figures developing our understanding of how cancer cells get through these barriers to pursue their metastatic journey. As the founding Chair of Cancer Biology at the MD Anderson Cancer Center, and professor and director of their Metastasis Research Laboratory, Fidler developed the theory of the 'decathlon' that metastatic cells have to complete to break away from one site and travel to, and then colonise, another.

Molecular scissors

To extricate themselves from the primary tumour and launch themselves into the circulation, malignant cells first have to degrade the extracellular matrix – dense and intertwined tissues designed to trap fugitives. To do this they use molecular scissors or hammers: metalloproteases (MMPs). MMPs, especially MMPs 1 and 2, are crucial for invasion and metastasis. MMP2, also called 'gelatinase', has the specific function of destroying basement membranes and degrading collagen IV, which provide the containment structures for organs and blood vessels.

Proteases remain among the most interesting molecules to block, but developing drugs specific to that target has so far proved very difficult. The approach currently favoured is to act indirectly on the proteases by targeting the growth factors that stimulate them.

Travelling in disguise and in company

A transformed epithelial cell can 'disguise itself' as a mesenchymal cell, a simulated fibroblast, to ease its escape. Epithelial–mesenchymal transition (EMT) contributes to development of the embryo and tissue repair, but it also promotes carcinoma progression – an oncofoetal programme.

Issues in targeting EMT for better therapeutic response in carcinoma were presented at the virtual AACR by Jean-Paul Thiery, visiting professor at the Department of Clinical Oncology, at Hong Kong University. His internationally renowned studies address mechanisms of resistance driven by intermediate EMT states in carcinoma; they focus on strategies to restore immune response, with the ultimate goal to apply EMT-based therapeutic approaches in clinical trials.

A cell metastasises more easily if, in exiting the primary site into the circulation, it is accompanied by fibroblasts or other cellular elements of the stroma. This is a further example of cancer forcing 'good cells' to 'commit a crime'.

Similarly, the cells of the immune system, in particular innate immunity, macrophages and neutrophils, can also become allies in the metastatic process. Zena Werb, former Professor and the Vice Chair of Anatomy at the University of California, San Fran-

cisco, who sadly died in June 2020, did the early work showing that components of the extracellular matrix are involved in signaling. She used fluorescence microscopy to demonstrate how 'mad macrophages' dance along the edge of a neoplasm, making the molecular scissors, MMP9, and degrading collagen IV, thereby favouring the detachment of cells to start their metastatic journey.

Constructing invasion routes

A tumour's capacity to manufacture its own blood vessels, or to divert them in its favour to receive oxygen and nutrients – the process of angiogenesis – is well known. Those same 'pirated' circulation channels – the capillaries promoted by the tumour itself – are also used to transport 'emissaries' from the tumour to enable malignant cells to navigate to, and then colonise, the distant organ that is their final destination.

Against this process of capillary generation, which is indispensable for metastasis, clinicians have at their disposal a battery of effective weapons, including bevacizumab, which has proved to be the most universal and powerful anti-angiogenic, and aflibercept. However, it has not been as universally effective as had initially been hoped.

At the AACR meeting, Robert Kerbel, from the University of Toronto, Canada, who has a long-standing research interest in anti-angiogenics as a potentially less toxic way of treating advanced cancers, addressed some of the challenges to their effective use. He highlighted the risk that, used for prolonged periods, anti-angiogenics may become blunt weapons, or may even stimulate metastasis. He proposed the need for 'modernising' the way they are used, arguing specifically that it may be necessary to use them as prolonged, maintenance therapy or in combination with immune therapy.

Preparing the new site for colonisation

In the target organ – liver, lung, brain, bones – welcoming 'niches' are formed, where the tissue is particularly suitable to accommodate metastases. It is very difficult to explain why one group of malignant cells chooses one organ to colonise over another. Sometimes a metastatic cell enters the vessels of an organ, but it does not stop there, preferring to pass through to the next destination. Growth factors, immune system cells, mesenchymal stem cells all play a role in preparing a particular tissue to offer a cosy home for metastases.

At the AACR meeting, Harold F. Dvorak, an 'icon' of tumour progression, who defined cancer as 'a wound that never heals', and discovered the of role fibrin (a protein involved in blood coagulation) in tumour growth, highlighted the importance of vascular permeability in tumour stroma generation and wound healing. Fibrin helps cells to form scar tissue, and also helps cells move around. Vascular permeability factor – also known as vascular endothelial growth factor – makes endothelial cells migrate and grow.

The hostile environment strategy

An important innovative therapeutic strategy based on 'getting around' the tumour – as opposed to attacking it head on – emerged as a key theme from many lectures and sessions at this AACR meeting. Such a strategy would seek to deprive malignant cells of the support they need from their microenvironment, by modulating, specifically and selectively, cells that under normal circumstances act as our 'allies', but in 'criminal association' with cancer can turn against us to support the malignant cells.

These 'criminal associates', which are what make the metastatic niche so comfortable for the metastatic cells, include endothelial cells, capillaries and inflammatory infiltrate, and lymphocytes. The presence there of numerous innate immunity cells, that are hyperstimulated and become inflammatory and pro-angiogenic, weakens the adaptive immunity component, which is no longer able to kill the tumour, as described by Michael Karin during the lecture for the Clowes Award for Outstanding Basic Cancer Research

This opens up the potential for therapeutic strategies aimed at targeting the tumour microenvironment by administering molecules that inhibit angiogenesis, to block the nourishment and metastasis pathways of the tumour, and that stimulate the immune system and redirect the immune response from playing a pro-tumour pro-inflammatory role to its 'well-behaved' role of fighting the tumour,

All credit to AACR CEO Margaret Foti and her staff for creating and giving life and content to an exceptional international 2nd virtual meeting, during the COVID-19 pandemic, with around 40,000 participants.

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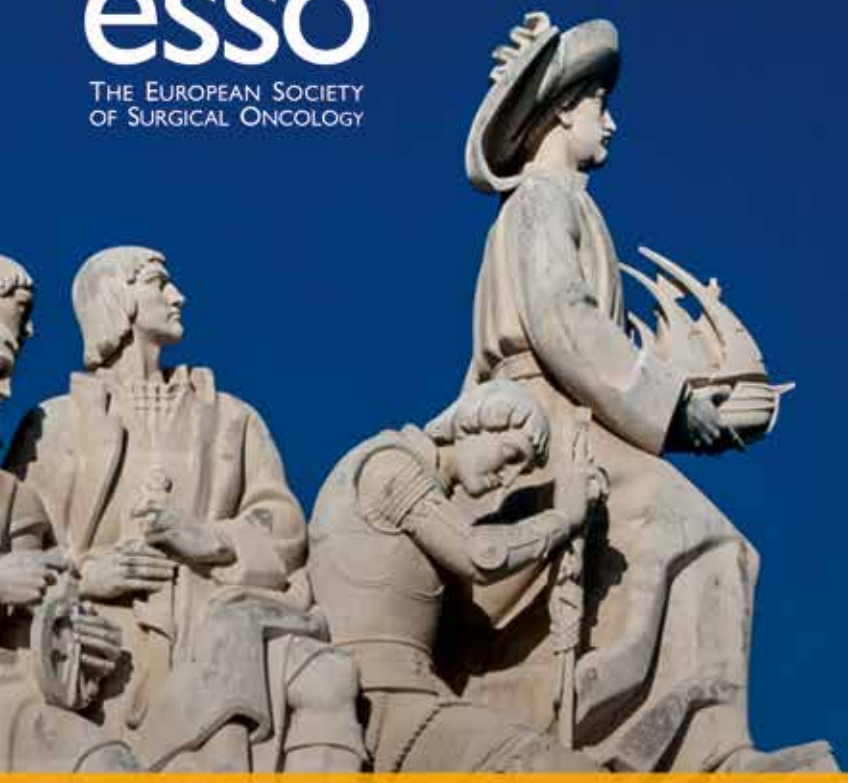

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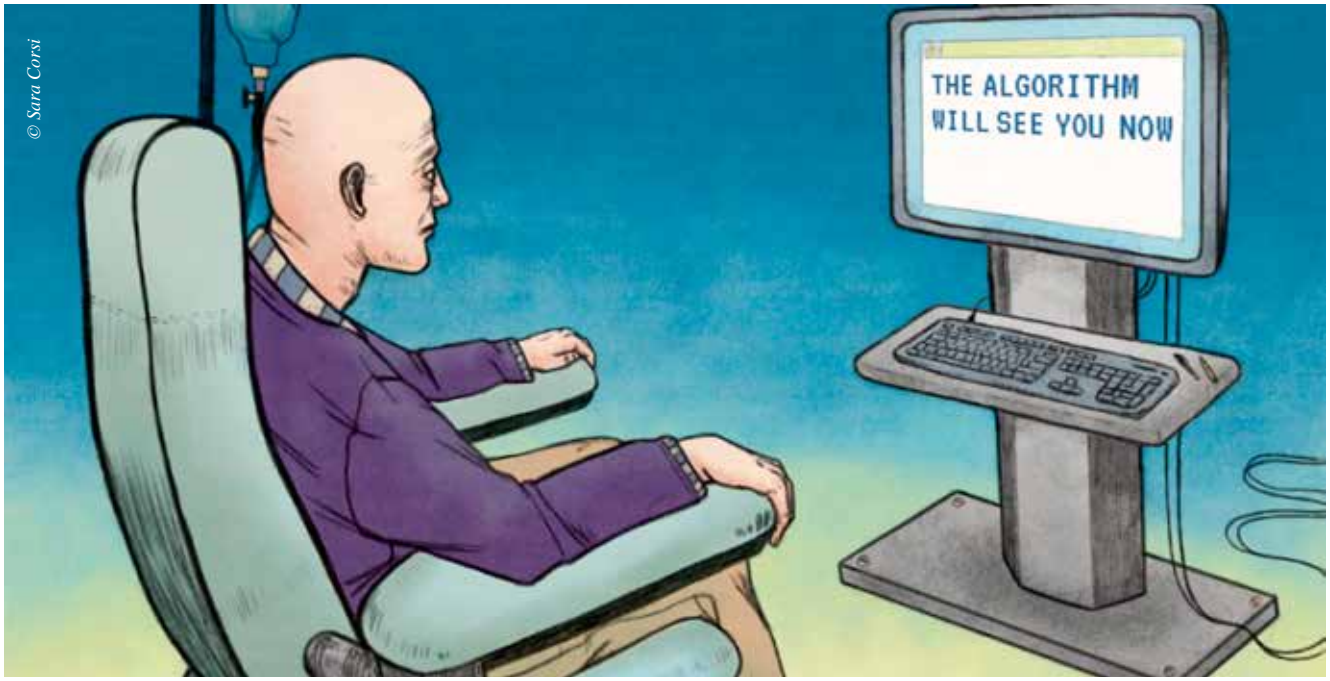

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Will artificial intelligence revolutionise cancer therapeutics and care?

Artificial intelligence (AI) has started to impact oncology, with tools for quicker and more-accurate diagnostics, but its role in better interpreting genomic data is still to be realised. **Rachel Brazil** pinpoints the latest avenues where AI is gaining ground, and explores its potential to empower future oncologists with new approaches to clinical decision making.

The first machine learning application in healthcare was approved by the US regulator as recently as 2019 to analyse MRI images of the heart. In oncology, applications that make use of artificial intelligence (AI) are appearing thick and fast, from improving diagnostics to developing new biomarkers. The algorithms being developed could lead to significant advances and cost savings, but this is a field with a history of over-promising. So what can AI do in both diagnostics and therapeutics and how is it currently helping decision making? And what role will AI play in future developments of precision oncology? Could it provide the tool to interpret the massive amounts of genomic data becoming available and provide us with insights that can ultimately improve patient care?

Artificial intelligence has a rocky

history dating back to the 1950s. In 1997, IBM's Deep Blue computer defeated chess champion Garry Kasparov, and by 2011 IBM's new Watson supercomputer was able to win the $1m prize in the US game-show *Jeopardy*. The quiz competition presented contestants with general knowledge clues in the form of answers, and they had to phrase their responses in the form of a question. This progress came from advances in machine learning, where a computer can be 'trained' to find patterns on sets of data and then apply this knowledge to new data. This has now advanced to deep learning, whereby systems are able to improve their performance or 'learn' when exposed to sets of data, and can essentially programme themselves.

AI in diagnostics and treatment

One of the first areas in oncology to take advantage of AI was diagnostic radiology, where it has the capacity to hugely reduce the workload of radiologists. Therapixel, a French AI software company, has developed an algorithm to interpret mammograms, called MammoScreen, which is now approved in the US and currently completing European regulatory requirements. Using deep learning technologies, the algorithm was trained to recognise cancer lesions on hundreds of thousands of previously confirmed cases. This will mean that the standard practice of having two radiologists inspect each mammogram can be replaced by one radiologist and the algorithm, which should reduce the time for a diagnosis.

In January 2020, Google Health published results showing their algorithm out-performed six radiologists, with fewer false-positives and false-negatives (McKinney SM, Sieniek M, Godbole V et al. *Nature* 2020). Their DeepMind supercomputer was trained on de-identified mammograms from the UK and US, and showed a 5.7–1.2% reduction in false-positives when tested on new data, and a 9.4–2.7% reduction in false-negatives. "One thing that gives our AI system an edge is its large training set: over 70,000 mammograms, including more than 7,000 cancers. This is certainly more than a typical radiologist would encounter during their training," says Software Engineer and lead Google Health author Scott McKinney.

"The indications from our early research is that the system can distinguish different tissue types with very high confidence – and in a matter of minutes"

It is not clear why the AI model does better. "We're still investigating what perceptual features might drive this improvement," says McKinney. "We do know that the mistakes made by humans and the AI system are not perfectly aligned. For instance, when we showed cases to six independent radiologists, there were cancers that all radiologists missed, but the model caught. Conversely, there were also instances that all six radiologists saw, but the model missed." He sees this as a positive outcome that would allow for a superior combination of human and machine judgement. In August 2020, a study by researchers at the Karolinska Institute and University Hospital in Sweden that compared three different AI algorithms to identify breast cancer on previously taken mammograms demonstrated "that one of the three algorithms is significantly better than the others and that it equals the accuracy of the average radiologist," (Salim M, Wåhin E, Dembrower K, et al. *JAMA Oncol.* 2020).

Another AI model is being developed by Canon Medical Research Europe, in collaboration with Kevin Blyth of the University of Glasgow, to provide more accurate measures of tumour size in mesothelioma, an aggressive cancer of the lung lining. "It grows around the lung like the rind of an orange, so it's a very difficult tumour to measure," says Blyth. The task is too time-consuming for radiologists, who use much cruder size assessments, and this can make it complicated to assess whether a patient has responded to a treatment. The hope is that AI will provide a solution. Blyth's team has trained an algorithm to analyse CT scans and volume segment each individual image to find the total tumour volume. They are now ready to test the algorithm on new data, which will be collected as part of a pan-European mesothelioma research network funded by Cancer Research UK.

As noted in a recent article in *Cancer World* (cancerworld.net 15 June 2020), the use of AI has been best displayed in diagnostic dermatology, where AI outperformed expert dermatologists in diagnosing

melanomas. However, diagnosis isn't the only area where AI is providing support. In 2020, Steve Jiang from UT Southwestern Medical Center, used enhanced deep-learning models to create optimal radiology plans. As it is important to start radiation treatment as soon as possible in many patients, the ability to quickly translate complex clinical data into a radiology plan could streamline the process. Jiang's study showed an AI algorithm could instantly render 3D radiation dose distributions for each patient. Trained on data from 70 prostate cancer patients, four AI models were able to predict the clinicians own calculations. UT Southwestern now plans to use these models with patients (Nguyen D, McBeth R, Sadeghnejad Barkousaraie A, et al. *Med Phys* 2020).

A team at IBM Research in Dublin are also looking at how AI can assist surgeons. "Our goal is to provide a surgical team with live tissue classification interactively, during surgery," explains team member Pol Mac Aonghusa, "think of it as having virtual pathology capabilities available during surgery to help the surgeons distinguish between tissue that is healthy, benign or cancerous."

The team has developed and trained an AI algorithm that can interpret subtle differences in the dynamic perfusion patterns of fluorescent dyes in real time (Zhuk S, Epperlein JP, Nair R et al. *Proc MICCAI* 2020). "The indications from our early research is that the system can distinguish different tissue types with very high confidence – and in a matter of minutes," adds Aonghusa, so "the potential is for more effective, less invasive surgeries with less post-operative complications."

The AI genomics revolution

The biggest impact is likely to be seen in the interpretation of genomic data, according to Parker Moss, Chief Commercial & Partnerships Officer at Genomics England. So far AI is mainly being used in a 'supervised learning' capacity – that is, to do something a human does, but more efficiently. But Moss argues that "the more exciting area of machine learning and the much more disruptive area is 'unsupervised learning', where you have it look at complex data sets and don't know what you're looking for."

Genomics England was set up by the UK National Institute for Health Research and NHS England, and other medical charities, to sequence 100,000 whole genomes that would give insight into rare diseases and common cancers. Using this data with novel AI algorithms, they hope their collaborators will come up with patterns that might better predict the appropriate treatment or provide a more-accurate prognosis.

"It is not just the 22,000 genes [in the genome], but it's the complex gene networks," says Moss. "That's where machine learning comes in. [It's] very good at identifying signal in complex data and [the] whole genome is about the most complex data item you can get from an individual patient." Gerstung agrees we are reaching the era where we have sufficiently large genomic data sets to train complex algorithms to understand the unique mutational distributions along chromosomes that can be characterised as tumour subtypes.

One project Genomics England funds is a partnership with precision AI platform company Cambridge Cancer Genomics (CCG.ai) who are developing a sequencing panel that will cost-effectively profile the overall tumour mutation burden (TMB) – the total number of DNA mutations in cancer cells. Patients with a high number of mutations are more likely to respond to certain immunotherapies. They hope this will allow them to assess DNA in the blood and use a 'liquid biopsy' approach, rather than having to repeat tumour biopsies and whole-genome sequencing.

"I see this more as a timing challenge – rather than a fundamental incompatibility between AI and medicine"

Computational biologist, Moritz Gerstung, from EMBL's European Bioinformatics Institute (EMBL-EBI) in Cambridge, UK, has been taking the image recognition used in analysing mammograms one step further and has found an algorithm that can infer genomic information from histology slides. "The algorithm that we used was originally developed by Google to recognise everyday objects on the internet that range from an Irish Setters to 'Spaghetti alla Carbonara'," he says. But now it is able to identify more than 160 recurrent DNA mutations, and thousands of RNA alternations in a tumour. Together with researchers from the Wellcome Sanger Institute and

Addenbrookes Hospital in Cambridge, Gerstung has combined digital pathology with machine learning by training his algorithm on more then 17,000 digital histopathology slides covering 28 cancer types (Fu Y et al. *Nat Cancer* 2020).

"[The digitized slides were] a bit of a sleeping beauty, because, while people have extensively analysed all the different layers of molecular data, they hadn't really taken such a deep dive into the histopathological slides and how these could be related to genomic makeup," says Gerstung. The algorithm is able to analyse features such as nucleus size, size distribution and irregular positioning, at a statistical level – something not easily done by a human. "We found an association roughly for 20% of the genomic alterations," he says, but predicts with more data their algorithm would identify even more associations. Whilst this isn't a replacement for genetic testing, Gerstung says there may be situations when this could act as a diagnostic tool, and he hopes that it may be ready for the clinic within a couple of years.

Other groups are targeting specific genetic features, such as identifying microsatellite instability (MSI) in colorectal cancer, based on routine histology slides (Kather JN, Heij LR, Grabsch HI et al. *Nat Cancer* 2020). "It would save the sequencing cost and, even better, you could go through the back catalogue of patients who had already had a digital pathology image made of their tissue and may now be eligible for a drug which has come to the market based on their MSI," says Moss.

IBM Watson Health, AI and genomics

IBM was an early player in AI, naming its supercomputer Watson after IBM's founder and promising to bring AI directly into the clinic to support oncologists with therapeutic decision making. It claimed that using natural language processing to extract information from peer-reviewed articles it could match genetic alterations in a patient's tumour with the most relevant therapies and clinical trials, matching or surpassing the clinical decisions made at top institutions.

But the path has not been smooth for IBM Watson, and early indications suggested it would struggle to meet the expectations it had set. Reports in 2017, from a partnership with the Memorial Sloan–Kettering Cancer Center in the US, documented that Watson had difficulty distinguishing between cancer types and gave incorrect treatment options, such as suggesting patients with severe bleeding be treated in ways that would exacerbate the bleeding. Another US partnership with the MD Anderson Cancer Center cost $62 million and was never actually tested on patients.

The past few years have shown signs of renewed confidence. In 2017, IBM and the University of North Carolina published the first paper on Watson's effectiveness, showing Watson spotted potentially important mutations not identified by a human review in 32% of cancer patients enrolled in the study (Patel NM, Michelini VV, Snell JM et al. *The Oncol* 2018). In 2019, IBM signed a partnership with the University Hospital in Geneva (Hôpitaux universitaires de Genève, HUG) to use IBM's Watson, making it the first university hospital in Europe to use the tool, which IBM says completes an analysis of a whole genome and RNA-sequencing results in 10 minutes, compared to the 160 hours it would take to do this manually. Whether this new initiative will be successful remains to be seen. HUG did not respond to requests for information on the partnerships' progress and IBM Watson Health were unavailable for comment.

Challenges ahead

There is still scepticism around the clinical use of AI. One thorny issue is that of inbuilt biases. How the system learns will depend on the data used in its training. For example, when AI has been used to predict a person's age from an image, accuracy varies across ethnicities, unless the system is trained using racially diverse data sets. Google's model for analysing mammograms worked across data from the UK and US, but McKinney says they realise it may not be representative of all women around the world: "We're actively sourcing diverse new datasets to promote the inclusiveness of our technology," he says.

The potential to exacerbate existing health inequalities in groups that are already under-served was pointed out in a recent report on AI for genomic medicine by the PHG Foundation, a Cambridge University think-tank. The other major issue with AI has become known as the 'black box' problem. The nature of deep learning algorithms means we often don't actually know how they produce their predictions – it's effectively a black box. "That's problematic, although not insurmountable,"

says Philippa Brice, External Affairs Director at PHG, "AI still produces some major errors," she adds.

In a talk at ETH Zurich in October 2017, Olivier Verscheure set out some of the problems still apparent in AI. Verscheure is head of the newly created Swiss Data Science Centre, a joint venture between Swiss universities ETH Zurich and EPFL. He described how easily AI algorithms could be fooled. A recent image recognition test trained an AI system to recognise pictures of socks, but when only a few pixels of such an image were altered, the best algorithms identified the image as an Indian elephant. It certainly shows there is still a need for human supervision in areas such as cancer diagnosis, where it's important to understand the basis of any decision.

"I see this more as a timing challenge – rather than a fundamental incompatibility between AI and medicine," says Aonghusa. "Like any new technology, a certain air of mystery surrounds the workings of some AI algorithms. But this is changing generally, and it's fair to say that improving the explainability and trust in AI is one of the hottest topics in AI research." The new ambition is for 'white box AI' – interpretable models where we understand the variables that influence them. For example, Aonghusa says their algorithm used to classify cancerous or healthy tissue is based on well understood physical values, with no hidden layers or complex parameters.

Combining human expertise with AI

For the time being, AI is likely to be limited to specific data-heavy tasks, "which it will probably do better than a human," says Blyth, "but a human will still do more-complex tasks more naturally." So whilst his algorithm may more consistently analyse tumour volume in a mesothelioma patient, only a human can currently look at the same set of images and see that the disease has spread to other areas.

"That's where the problem comes… it's a good servant, it's a great servant, but a bad master"

Ultimately Gerstung says "[we] should not think so much about AI, but rather about intelligence augmentation…at the end of the day, it will have to rely on an expert to make the definitive diagnosis, and I don't see that this will change anytime soon." But it certainly has the capacity to free physicians from administrative, clerical tasks so they can focus on the uniquely human work of connecting with patients.

What AI may stimulate is a new type of clinician. "I think it is changing the face of medicine," says Brice, "I think we do need new supporting health professions, scientists who can explain and interpret data to aid the clinicians." But Aonghusa says he can't see AI fundamentally changing things: "the role of the physician has continued to evolve for hundreds of years. It has continuously adopted and applied new technologies from germ theory to antibiotics – AI should be no different." He says from his experience of working with trainee surgeons, the adaptation to AI and the opportunities it promises is already occurring.

Nevertheless AI is likely to increase the push towards more interdisciplinary medical teams, according to Genomics England, together with a more joined-up approach to clinical practice and clinical research. "For machine learning to have an impact, the two worlds of research and clinical care have to come together.

That's very much what Genomics England are trying to do," says Moss. He describes a "virtuous infinity loop," where the patient consent to use more data as a resource for machine learning will drive diagnostic and therapeutic advances that will then encourage more clinicians to use it.

Obviously the use of massive amounts of patient data brings up the issue of ethics and consent. Genomics England stress their debt to the 100,000 participants who have agreed to contribute their detailed medical records, albeit anonymised. "[We] do everything we can to reassure participants, that their data is being used for the right purposes in a safe and secure environment," reassures Moss. This includes communicating to patients how AI works, which he says "can be conceptually difficult to understand."

AI and machine learning offer unique possibilities in oncology, but says Brice "the danger we have to resist all the time, with all these technological advances, is to think it's the solution to everything and we don't need to think about how to use it. That's where the problem comes… it's a good servant, it's a great servant, but a bad master."

European Association of Urology

Early detection of prostate cancer – Europe's chance to save lives and increase quality of life for prostate cancer patients

For a number of years now, the European Association of Urology has been working with patient cancer organisations to raise the profile of prostate cancer in EU policies and activities. With the EU Cancer Plan, the European Commission has a unique opportunity to take forward the fight against prostate cancer and to build consensus, so that together, we can beat this disease.

Why is prostate cancer an important condition for the EU to address? Well, first and foremost, prostate cancer is a serious European public health issue that has a significant impact on patients and their families, and on health systems across Europe. Prostate cancer is the most common male cancer, and killed 107,000 men in Europe in 2018; it is thus not an indolent disease. It is responsible for 10% of all male cancer deaths and is the second cause of male cancer death before colorectal cancer. Today, prostate cancer kills more men than breast cancer kills women.

Despite this significant public health burden, relatively little is performed at EU level on prostate cancer, particularly in comparison to breast, cervical and colorectal cancers, which have all benefited from technical guidelines from the European Commission on early detection (on the basis of a mandate from the European Council Recommendations in 2003 on cancer screening).

Earlier in 2020, in order to respond to the consultation on the EU Cancer Plan, we joined forces with Movember, Europa Uomo, the European Cancer Patient Coalition and the European Alliance of Personalised Medicine to update our 2017 White Paper on Prostate Cancer. This updated White Paper gives recommendations on how the EU Cancer Plan can tackle prostate cancer.

One clear recommendation from the White Paper is to add prostate cancer to the list of cancers that benefit from European Commission supported guidelines on early detection. The evidence is clear: early detection of prostate cancer in well-informed men saves lives, improves quality of life and reduces costs for health care systems. We would like the EU Cancer Plan to tackle EU wide guidance on this, as it has done with other cancers in the past.

The early detection of prostate cancer has been controversial because the use of PSA testing (that is the test that measures the amount of prostate specific antigen (PSA) in the blood to estimate the risk of prostate cancer in men) has led to a drop in mortality rates, but has come at the cost of over-diagnosis and overtreatment.

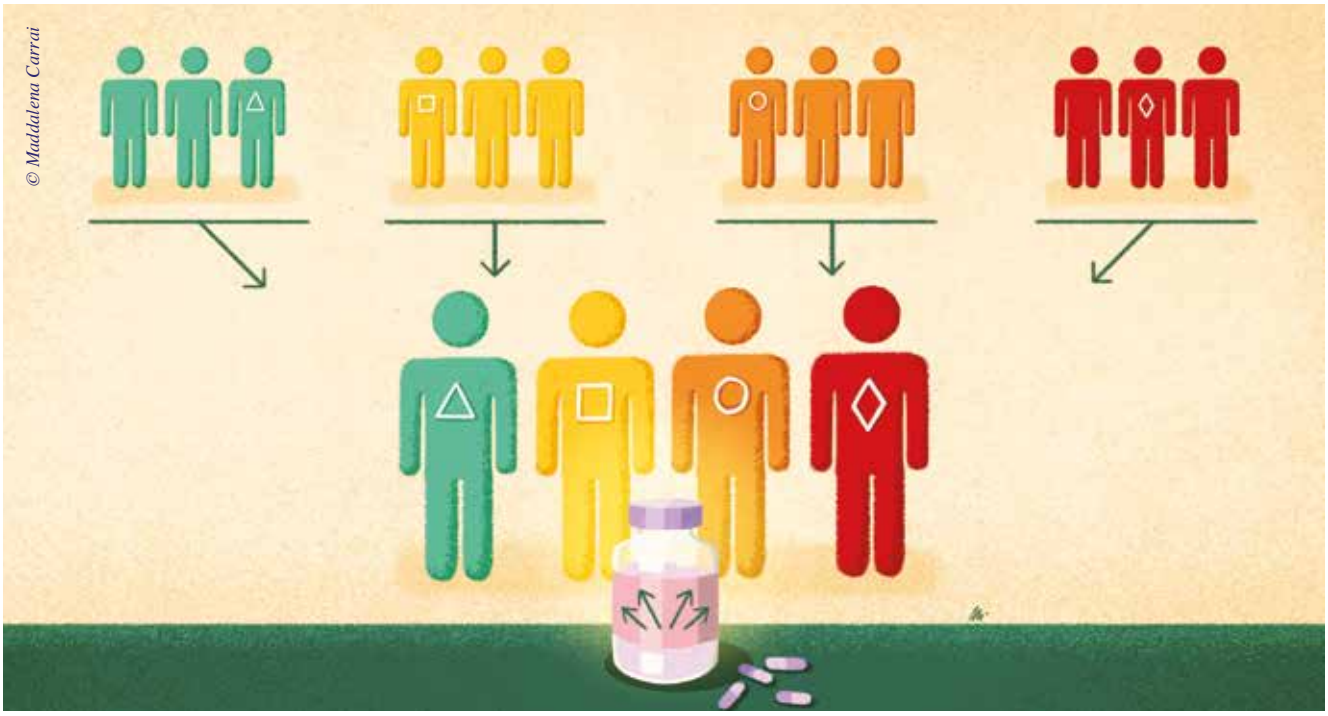
The most updated scientific evidence supports the use of PSA in early detection of prostate cancer with a risk-adapted approach in informed men, thus avoiding over-diagnosis and overtreatment. PSA can now be used more cleverly with Magnetic Resonance Imaging (MRI) and further risk stratification (using risk calculators which are freely available on the web) in men at higher risk. This combined approach will allow a substantial reduction of over-diagnosis and the number of men who need to undergo biopsy. Also, with the application of MRI-guided active surveillance for all low- and some intermediate-risk prostate cancers, the monitoring of patients can happen less invasively. This approach is reflected in the multidisciplinary 'EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer' https://uroweb.org/guideline/prostate-cancer/.

The EU Cancer Plan offers the European Commission a unique opportunity to tackle this issue and support EU member states to deliver consistent and clear guidelines on early detection of prostate cancer. By doing this, it can save lives and increase quality of life outcomes for patients across Europe.

We invite anyone interested in this subject to join us on 17 November at 17h30 for a virtual event on prostate cancer in the EU Cancer Plan, focusing on early detection. For more registration and more information on the event and the prostate cancer campaign, please see epad.uroweb.org.

EPAD European Prostate Cancer Awareness Day

RECOMMENDATIONS FOR THE EU CANCER PLAN TO TACKLE PROSTATE CANCER



Are tumour-agnostic approaches the future for oncology?

Never mind what or where it is, just look for the target. **Rachel Brazil** asks whether this will be the new paradigm for treating cancer, and explores the challenges raised by a tumour-agnostic approach when it comes to developing the clinical evidence, defining the value of the drug, and rolling out affordable and reliable diagnostics.

According to Francesco Pignatti, Head of Oncology at the European Medicines Agency (EMA), the term 'tumour agnostic' is a misnomer. The definition of agnostic in ancient greek, he argues, is 'lacking in knowledge'. But with these new approaches, it's not that we don't know, "it's a situation where we have comprehensive evidence, so in a sense, it's a very gnostic situation!" Nevertheless, 'tumour agnostic' (or 'tissue agnostic') is a term that has stuck to describe therapeutics that treat the molecularly targetable abnormalities that fuel cancers across multiple tumour types.

This approach has the potential to completely change the way patients are treated, but there are

questions about how our regulatory and health systems would need to adapt to this new paradigm.

In 2017 the US regulatory authority, the FDA, granted accelerated approval for the use of pembrolizumab (Keytruda), a programmed death receptor-1 (PD-1) inhibitor, for treating solid tumours that are either microsatellite instability-high (MSI-H) – where the cancer cells have a high number of mutations within tracts of repetitive DNA known as microsatellites – or DNA mismatch repair-deficient (dMMR) – where the cells are unable to repair mistakes made during the division process, leading to accumulations of mutations.

This represented an expansion from its previous approval for metastatic melanoma, metastatic non-small-cell lung cancer (NSCLC), head and neck cancers, and classical Hodgkin lymphoma. From five clinical trials, the drug was also judged effective for endometrial cancer, gastric cancer, pancreatic cancer and biliary cancers, where appropriate biomarkers were present.

The first FDA tumour-agnostic approval for a drug not already in use came in 2018, with the tyrosine kinase inhibitor larotrectinib (Vitrakvi). It was approved to treat any advanced solid tumour with mutations in the NTRK genes that drive tumorigenesis. The pivotal study showed an impressive 75%–80% overall response rate in 12 different cancer types that all had NTRK fusions (Drilon A et al. *NEJM* 2018). In August 2019 the FDA approved another tumour-agnostic drug, entrectinib (Rozlytrek), for treating metastatic solid tumours that have an NTRK gene fusion, where no alternative therapy exists, and metastatic NSCLC with fusions in the ROS1 gene. By 2019, the EMA had followed suit and granted larotrectinib its first tumour-agnostic approval.

At least 10 further tumour-agnostic therapies are in development, based on a range of genetic mutations, including mutations in the RET gene, found in 2.21% of all cancers, and mutations in the neuregulin 1 gene (NRG1), which is found across solid tumours in lung, pancreas and breast tissue. But whilst tumour-agnostic approaches have attracted a lot of attention, it is still a niche area. "The amount of companies and developers who claim that they are pursuing such development for the time being is relatively small, and whilst we cannot foresee the future, many think that this is not going to be the predominant approach," says Pignatti.

Clinical development – basket trials

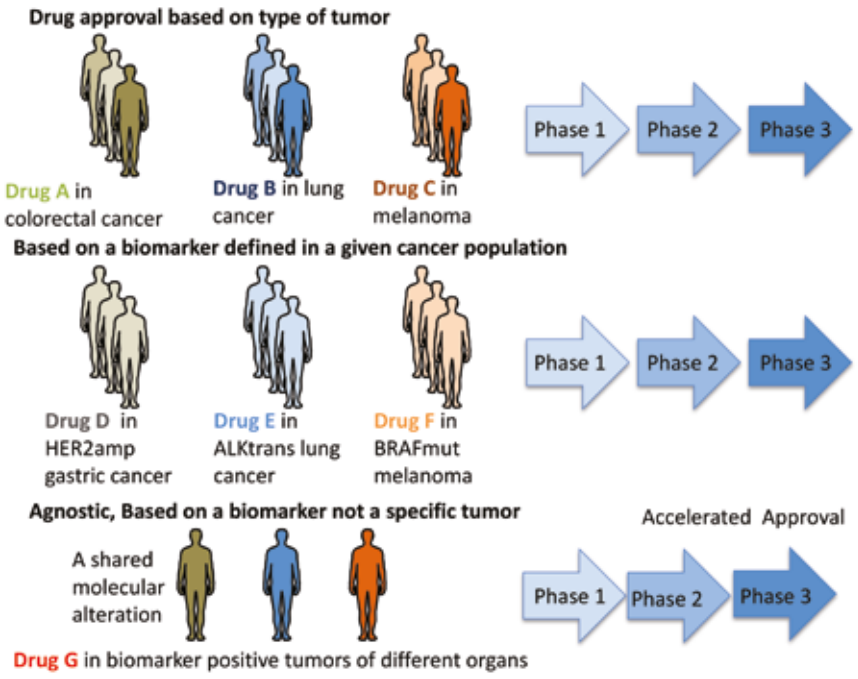
One of the innovations needed to develop tumour-agnostic drugs has been clinical trials that can span multiple histologies. These are known as basket trials (or sometimes bucket studies). They are currently done in multiple ways, but all governed by an overarching master protocol, often with specific treatment 'arms' or 'baskets' for cancers of different origins. "I've seen in practice different examples… you can decide how independent the different sub-studies are. You can have one sub-study for breast cancer and another one for lung cancer, or have one single study where you pull them all together," says statistician Olivier Collignon, from the Luxembourg Institute of Health, who is co-author of a study on statistical and regulatory perspectives on basket trials (Collignon O et al. *Clin Pharmacol Ther* 2020). Another new type of trial, an umbrella trial, studies multiple therapies in different biomarker-matched patient subgroups with the same cancer histology.

"What we like in this type of trial is that it allows us to apply the concept of 'leave no one behind', so you try to offer as many solutions as possible"

Whilst these trials are currently more common in exploratory phase II settings, they have started moving into the regulatory setting. One of the first basket trials used for approval was for vemurafenib (Zelboraf), approved by the FDA in 2011 for treatment of melanoma, based on the BRAF V600E genetic mutation. A basket trial also concluded that patients with the rare blood cancer Erdheim-Chester Disease who carried a BRAF mutation could also benefit from the drug (and approval for that indication was granted in 2017).

Large basket trials are becoming a key feature in oncology trials. "It allows [us] to be more efficient, but also [it allows] better partnerships," says Denis Lacombe, Director General of the European Organisation for Research and Treatment of Cancer (EORTC) in Brussels. An example is the 'Basket of Baskets' trial run by Cancer

The evolving framework of clinical trials used to support oncology drug approval



Trials have shifted from enrolling (*top*) unselected patients exclusively based on the type of tumour, to an exquisite, appropriate selection of biomarker-defined populations, either (*middle*) within a specific tumour type or (*bottom*) across a variety of different cancers that share a common molecular abnormality. Consequently, phase 3 clinical trials have been gradually replaced by redesigned phase 1 and phase 2 clinical trials, recently leading to accelerated and conditional approvals of new anticancer agents based on the results of phase 1/2 'basket' trials and large expansion cohorts of molecularly selected patients, thus redefining the traditional phase 1/2/3 model that previously worked with cytotoxic chemotherapies.

Source: Adapted from: C Hierro et al (2019) *Clin Cancer Res* 1:25:3210–3219

Core – a collaborative group of seven centres of excellence spread across France, Spain, Italy, Germany, Sweden, the Netherlands and the UK. The trial is currently testing the novel PD-L1 immunotherapy drug, atezolizumab. It aims to screen 1,000 patients over two years from patients treated at the seven centres, using a common molecular profiling platform to match patients to targeted therapies. The trial will also add other new experimental drugs from other pharmaceutical companies that target different genetic mutations (Brana I et al. *JCO* 2019).

The EORTC has embarked on a biomarker-led umbrella trial called UPSTREAM, focused on head and neck cancer (carcinoma, squamous cell of head and neck). "There are multiple partnerships with several companies, so that we can try to match each cohort of patients with the most probable drug to benefit them," says Lacombe. "What we like in this type of trial is that it allows us to apply the concept of 'leave no one behind', so you try to offer as many solutions as possible"

One positive change being seen with tumour-agnostic approaches is the inclusion in clinical trials of patients with rare cancers. "Rare cancers have not been in the spotlight, they get less attention, and that [has been] one of the benefits of having the capacity to understand the biology of cancer," says Lacombe. For example, NTRK fusions are present in only 1% of solid tumours, but if histologies are looked at together, it makes a big enough market for drug development to be worthwhile – hence the development of larotrectinib and entrectinib.

Uncertain evidence – are the baskets too small?

But these new types of trials have led to some concerns. "If we are talking about trials designed to learn, for hypothesis generating and understanding the biology, I think that they may play a very important role, because they allow us to progress so rapidly," says Lacombe, but he adds, "When it comes to trials to conclude – to change practice – that's a little bit more difficult."

The unease comes from the relatively small amounts of data that

have been used in some tumour-agnostic basket trials. For example pembrolizumab was approved in the US based on five studies in 149 patients across 15 histologies, and larotrectinib was studied in three trials including 176 patients across 12 histologies – significantly less data for each tumour type than would usually be expected. "We've seen drugs coming on the market earlier and earlier, based on sometimes very small data sets. And it can be [an] innovation, but we have also seen a lot of examples where actually what was called innovation turned out not to be an innovation in terms of patient benefit," says Lacombe.

The challenge for regulators is the added heterogeneity when different histologies are considered together. Basket trials include rare cancer types that share biomarkers with much more common cancers. Not only are the numbers of patients involved very different, but they may have widely different prognoses. "A 10% or 20% improvement in prostate cancer sounds very low to me. Whereas if you take a 20% improvement in multiple myeloma, or [another] more aggressive cancer, the figure is the same, but from the regulatory point of view, it doesn't mean the same thing," explains the statistician Collignon. And as cancers of different origins currently have very variable existing treatment options, it makes the benefit–risk assessments for an entire group very difficult.

Pignatti says that using what were initially exploratory basket trials for regulatory approval "requires a rigorous and planned way to minimise statistical error." One critical issue is controlling what are known as type 1 errors – results falsely indicating that a therapy is effective, when it is not. The heterogeneity of basket trials increases this risk due to the multiplication of errors present in each sub-group and in comparisons across multiple treatment arms and multiple comparisons over time. Currently regulators mandate statistical errors must be less than 5%, and Collignon says basket trials are particularly prone to error inflations above this level.

The drugs approved on a tumour-agnostic basis so far have been given conditional approvals, which means they can be legally marketed if there is a reasonable expectation of effectiveness even if the data is not complete. The pharmaceutical company is then expected to carry out extensive follow-up studies. "There is more emphasis on post-marketing data generation… they're expected to systematically collect data on efficacy and safety, or histologies that were considered to be less well represented at the time of approval," says Pignatti.

The EMA does not currently have specific guidelines for the use of basket trials in tumour-agnostic therapies, but Pignatti says they are being developed. While it is likely that each case will differ and will need to be assessed on its own merits, it also seems likely that the traditional phases of clinical trials may start to change, with more emphasis on large basket trials designed to explore multiple cancers.

Uncertain value

"[An] elephant in the room is the cost of such agnostic drugs," says Roberto Salgado, a pathologist at the Breast Cancer Translational Research Laboratory at the Institut Jules Bordet, Brussels and GastHuisZusters Antwerpen (GZA) in Belgium. "Reimbursement agencies may not be willing to fund costly drugs, based on phase II trials, where the full solid cancer population would need to be tested [for the biomarker]." Pignatti agrees that assessing value could be a problem, given that many of the current tumour-agnostic drugs have been approved based on very little data on overall survival rates – information critical for evaluating cost-effectiveness.

In April 2020, England's National Institute for Health and Care Excellence (NICE) and Germany's Institute for Quality and Efficiency in Health Care (IQWiG) rejected larotrectinib (Vitrakvi), at £15,000 (almost €17,000) for a 30-day course, due to its uncertain cost-effectiveness, given the limitations of available data and the lack of any other similar drug with which to make comparisons. The drug could have been useful for an estimated 700 patients in England, and marketers Bayer claimed that the assessing authorities did not yet have the right methods to assess tumour-agnostic approaches.

Lacombe suggests one solution could be to scale costs to reflect this lack of data: "The cost should be proportional to uncertainty and eventu-

"The cost should be proportional to uncertainty and eventually be revisited when it is confirmed to be a true benefit to the patient and to society"

ally be revisited one way or the other, when it is confirmed to be a true benefit to the patient and to society"

Diagnostics

The failure of larotrectinib to get through cost-effectiveness assessments contrasts with the enthusiasm shown by NHS England chief executive, Simon Stevens, who told a conference in 2019 that the NHS must be ready to fast-track tumour-agnostic therapies and prepare for the diagnostic testing that will be required to identify genomic mutations. Tumour-agnostic therapies will rely on European health services having the capacity for this testing. "National healthcare settings are still not equipped to fund or organise a systemic analysis of all solid cancers for genomic aberrations," says breast pathologist Salgado.

Tumour-agnostic therapies will rely on health services having the capacity for this testing

France and the UK have prioritised the development of a next-generation sequencing infrastructure, but prioritisation and support for precision medicine diagnostics is still lacking, particularly for rarer mutations such as NTRK gene fusions. There is also little standardisation of approaches, says Salgado. "Not all laboratories use the same gene panel, which is also a prerequisite to test for specific genomic markers, meaning that a patient tested in centre X with panel Y, for potentially trial Z, may not be identified in another laboratory that uses another panel that does not contain that particular gene [biomarker]."

Another contentious issue is whether a particular diagnostic test should be developed to accompany a specific drug – known as a companion diagnostic. "I'm not in favour of linking drugs to assays, as this creates an unfavourable context for [the] development of new assays," says Salgado. "Why should a company promote another biomarker, which is easier to perform in laboratories and [may] be less expensive, if they have an assay approved with the drug?" From the patients' perspective, he adds, "it makes sense to integrate gene panels with as many genes as possible, so that national cancer registries have a collection of the most important genomic events in solid and haematological tumours, and patients don't have to fear that their tumour will be tested with suboptimal gene panels."

Salgado also points out that the integration of new biomarkers into diagnostic panels is severely hampered by the fact that developments are driven by industry, with few academically developed biomarkers integrated in daily practice over the past decades. "To make this happen more frequently we need to collaborate with industry and regulatory [bodies] early on in trial design, to integrate new biomarkers in drug-driven clinical trials," he says.

How tumour-agnostic can treatments be?

Practicalities aside, there are still also fundamental questions about the tumour-agnostic approach and how effective it will turn out to be. There are already several examples where a genetic marker turns out to have a different impact on the progression of a tumour, depending on its histology. Kinase inhibitors targeted at the BRAF oncogene, for example, have not been shown to be tumour agnostic. BRAF mutations are present in roughly 50% of melanomas and 10% of colorectal cancers, but only melanoma patients responded dramatically to BRAF inhibitors (Kopetz J et al. *JCO* 2010).

From Genentech's non-melanoma basket trial for the BRAF inhibitor vemurafenib in 2012, it was discovered that, in colorectal cancer, BRAF inhibition triggers the epidermal growth factor receptor (EGFR) signalling pathway that drives cancer proliferation – a pathway not active in melanoma (Prahallad A et al. *Nature* 2012). More recently, the FDA approved a combination of BRAF inhibitors with EGFR inhibitors for treating metastatic colorectal cancers.

Differences were also found in a multi-histology basket study of the pan-HER kinase inhibitor neratinib (Nerlynx) from Puma Biotechnology, which targets both HER2 and HER3 receptors and is approved by the EMA for treating HER2-positive breast cancer. The study found clinical responses in patients with breast, cervical, biliary, salivary, and non-small-cell lung cancers, but not in those with bladder cancer and colorectal cancer.

Even before tumour agnostic approaches, there have always been differences in drug efficacy amongst patient sub-populations such as by age-group, gender, and general health status, and Pignatti suggests that, for regulators, histology may

become just one more factor that needs to be considered. "Histology will be a question, but all the characteristics of a population will be looked at, and if they're not homogeneous, you need to ask the question: Are there sub-populations where it can be shown that the drug doesn't work? – and then we will have to review our concept of a pan-histology efficacy to something which is a little bit more specific."

For some clinicians, the focus on tumour-agnostic therapies is unjustifiably overshadowing other areas of cancer treatment. The issue has sparked differences in opinion in the oncology community. An analysis by Vinay Prasad at the Oregon Health & Science University in Portland found that only about 9% of patients with metastatic cancer will be eligible for a genome-targeted drug, and just 5% will benefit from the therapy. He says the enthusiasm surrounding the promise of precision medicine needs to be tempered (Marquart J et al. *JAMA Oncol* 2018).

Others say that a growing number of patients will benefit as more tumour-agnostic therapies are approved. In a *Science* article (published online 24 April 2018), oncologist David Hyman reported that Memorial Sloan Kettering Cancer Center, in New York, had tested tumours of more than 25,000 patients: 15% could already be matched to an FDA-approved drug; a further 10% could be matched to drugs in clinical trials, and a further 10–15% to drugs then in pre-clinical animal trials.

"For regulators, histology may become just one more factor that needs to be considered"

But is too much attention and funding given to these approaches at the expense of other important therapeutic avenues? "To some extent, I agree with this statement," says Lacombe. "Not everything is about drugs. It's also about improving our radiation oncology techniques. It's bringing new technologies to patients. It's also improving surgical approaches – cancer is a very interdisciplinary field, it's a disease that is treated by an interdisciplinary team, so we should look at the palette of treatments that we have."

Clearly the picture will never be as simple as one drug for one biomarker regardless of the cancer type. Tumour-agnostic approaches represent the next step in precision medicine and our improved understanding of cancer biology. But it may be that they will continue to be the exception rather than the rule. "There remains an array of uncertainties and we have to understand, actually, why some patients are not going to benefit," says Lacombe. "We should remain humble. We are making progress, but we should be conscious of our limits, and what we say out there to patients."

Selected tumour-agnostic drugs in clinical development

Agent	Target	Indication	Status
Pembrolizumab	PD1	MSI-H (MMR-deficient) solid tumours	Approved
Larotrectinib	TRK	Solid tumours with NTRK fusions	Approved
Entrectinib	TRK, ALK, ROS1	Solid tumours with NTRK fusions	Approved
Merestinib	MET, TRK	Solid tumours with NTRK rearrangements	Phase II
Atezolizumab	PDL1	Solid tumours with MSI-H, high mutation burden or alterations in DNA proofreading genes	Phase II
TPX-0005	TRK, ALK, ROS1	Solid tumours with NTRK, ALK and ROS1 rearrangements	Phase I/II
LOXO-195	TRK	Solid tumours with NTRK fusions, including those resistant to larotrectinib	Phase I/II
LOXO-292	RET	Solid tumours with RET rearrangements	Phase I/II
RXDX-105	RET	Solid tumours with RET fusions	Phase I
LY3300054	PDL1	Monotherapy in MSI-H solid tumours; various combination criteria	Phase I
PLX8394	Mutant BRAF and wild-type CRAF	Solid tumours with BRAF mutation	Phase I/IIa
PLX9486	KIT	Solid tumours with KIT mutations	Phase Ib/IIa
BLU-667	RET	Solid tumours with RET alterations	Phase I/II

Tissue-agnostic indications contingent on trial data

MMR – mismatch repair, MSI-H – microsatellite instability-high, PD1 – programmed cell death protein 1, PDL1 – PD1 ligand 1

Source: Adapted from: K Garber (2018) Tissue-agnostic cancer drug pipeline grows, despite doubts. *Nat Rev Drug Discov* 17:227–229

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Does it work for my patient?

A pragmatic approach to building evidence on clinical effectiveness

Momentum is growing behind efforts to ensure new cancer therapies do not enter the market without any strategy for developing the evidence that patients and their doctors need to make informed decisions on whether it is the best option for them. **Marc Beishon** reports.

Should patients be at the centre of attention in the development of new cancer drugs? It might seem extraordinary that this question is even asked – what else matters? But it is a question high on the agenda of the European Organisation for Research and Treatment of Cancer (EORTC) in its campaigning work on 'treatment optimisation'. This pan-European not-for-profit organisation is trying to ensure that the current wave of often very costly drugs are actually used in an optimal way for patients.

The aim is to optimise treatment by answering the many clinical questions not addressed in the traditional development and approval process. As initially set out in a paper co-authored by EORTC director Denis

Lacombe (*EJC* 2017 86:143–9), such questions include:

- How does a new treatment compare with the optimal therapeutic option in routine clinical practice?
- What are the clinical outcomes when the new treatment is administered in real-life cancer patients or in off-label indications?
- Would it be better to shift the focus to how to combine and/or sequence the new treatment with the existing therapeutic options?
- What is the optimal administration scheme/treatment duration and at which benefit/risk ratio?
- What are patient preferences regarding multiple therapeutic options?
- What are the long-term issues related to the treatment?

The EORTC has been promoting this agenda for several years, including in a Comment piece Lacombe wrote for *Cancer World* in October 2017 under the title 'Let's be honest, our research efforts centre on drugs not patients'. But it is also a consistent call by leaders across the clinical and patient advocacy cancer community, who have pointed out the neglect in funding academic or public trials that answer such questions.

"We must confirm the data like we do with new cars, which we crash to see if they are as safe as the manufacturers say," says Lacombe. "Why is medicine the only field where we accept so much uncertainty? There is a big price to pay for uncertainty by driving in the dark, and we will encounter big problems such as major toxicity at some point."

The lack of certainty regarding the risks and benefits of new drugs has increased recently owing to their number and to speedy approvals. American oncologist Vinay Prasad is among the voices who have been sounding the alarm about the design and reporting of registrational clinical trials, and of current regulatory approaches. In his new book *Malignant*, he contends that, in an era where surrogate markers are used for approvals, the two factors that matter most to patients – overall survival and quality of life – are being sidelined in many registrational studies and not followed up after approval. "Whether cancer drugs must show survival or quality of life gains before approval is debatable," he writes, "but no sensible person can think they should never show these gains."

"Why is medicine the only field where we accept so much uncertainty?"

Greater backing for change in Europe is now in train following the publication of a treatment optimisation manifesto by EORTC and a number of stakeholders, including the European Federation of Pharmaceutical Industries and the European Patient Forum. It was presented last year at a workshop hosted by the European Parliament's Science and Technology Options Assessment (STOA) panel, which had the aim of exploring how a framework for applied clinical research could close the uncertainty gaps generated by the existing system, especially in the era of personalised medicine.

Driving in the dark

As participants at the STOA event heard, 'driving in the dark' hampers efforts to focus healthcare spending on treatments that can make a real difference, and avoid wasting limited resources on treatments that offer minimal or no benefit. Wim Goettsch, a health technology assessment specialist at the National Health Care Institute in the Netherlands, who spoke at the event, points out that cancer is a particular concern, as oncology drugs typically have the biggest impact on budgets, and need to show they deliver value for money. The issue of cost and value is becoming more acute because of the escalation in the number of treatments used in managing the disease. "We have focused in the past on single agents, but now there are more combinations and treatment lines, so they end up being more costly in use than you might expect," he says.

"We see expensive new treatments such as CAR-T being used in practice earlier than say the third line that it is supposed to be used at, and also such treatments are used with other costly procedures such as bone marrow transplants," he adds. "And people can have treatments again when they relapse, so costs can be higher still. We need to look much more carefully at clinical practice as a result."

The key question is: what changes can realistically be made to give decision makers more direction on cost-effective practice? Previously, *Cancer World* has looked at the concept of real-world data – and how far it can be relied on to define the true benefit derived from treatments administered in clinical practice (cancerworld.net 7 June 2020). There are a number of platforms in Europe and the US that are gathering such data, together with initiatives to improve data quality of cancer regis-

tries. There has also been progress in grading the value patients get from treatments, such as with the Magnitude of Clinical Benefit Scale developed by the European Society for Medical Oncology (ESMO).

But the EORTC takes the view that the uncertainties are just too great to be solved with mining data. They argue for the need to ramp up so-called 'pragmatic' clinical trials – trials designed to evaluate the effectiveness of interventions in real-life conditions of routine practice.

The case for pragmatic trials

The idea of pragmatic trials is widespread in medicine, not just oncology. A simple definition is that they "are run in real-world settings, test interventions compared with usual care (rather than placebo), and are conducted in a way that seeks to enhance the generalisability of the results that they produce" (Haff N et al. *JAMA Netw Open* 2018). There are tools such as the Pragmatic Explanatory Continuum Indicator Summary 2 (PRECIS-2), which show whether a trial meets pragmatic ideals. But they can be hard to conduct, and face challenges such as dropouts.

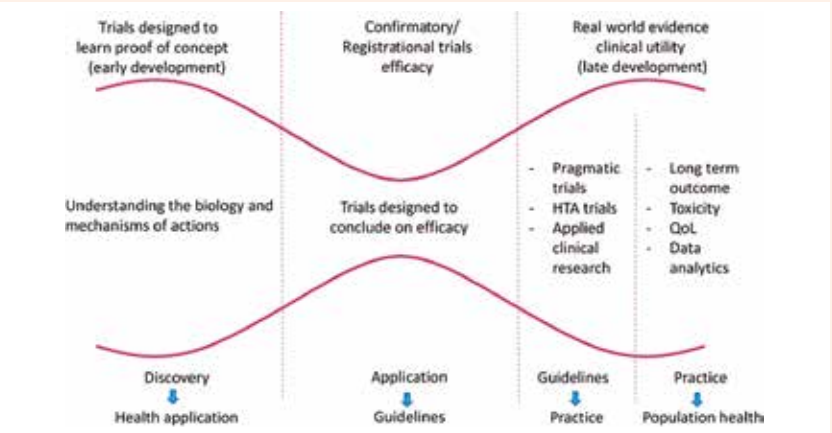
In oncology, the emphasis on optimising treatment mainly concerns new agents in what is more broadly defined as applied clinical research (and in the context of personalised or precision treatments). Lacombe and colleagues put forward a lengthy discussion in a paper in 2019 on the policy changes needed to create a continuum from basic biology to long-term population outcomes, in which an applied/pragmatic trial stage is a fundamental step, and not only for drugs but also for other oncology interventions (Lacombe D et al. *Mol Oncol* 2019).

As examples of the type of applied optimisation work needed, the paper mentions two randomised clinical trials, supported by independent funders, that have been examining optimal treatment duration of immunotherapies in melanoma. The examples are well chosen, as the lack of clarity about how to use these expensive therapies to best effect has been a concern for oncologists, patients and payers. New immunotherapies and BRAF inhibitors prompted a group in the Netherlands to establish the Dutch Melanoma Treatment Registry, and immunotherapies are also a subject for iPAAC, the third European Joint Action on Cancer (2018-2021), in its work package on innovative cancer therapies, as they "reflect the many challenges faced regarding the proper use of cancer drugs".

While much of the concern is about new agents, there are examples of long-standing oncology practices that were eventually shown to be not effective and even harmful, as timely follow-up trials were not

There are examples of long-standing oncology practices that were eventually shown to be not effective and even harmful

A framework for clinical development of new drugs



This framework for clinical development of new drugs, presented in a review article in *Molecular Oncology* in 2019, aims to ensure the process generates evidence on 'the most relevant clinical outcomes: namely quality of life and patient survival'. The paper was a collaboration among authors from the EORTC, NICE Scientific Advice (UK National Institute for Health and Care Excellence), the Institute of Cancer Policy at King's College London and the University Hospital of Saint-Luc Catholic University of Louvain, Brussels.

Source: Denis Lacombe et al (2019) Late translational research: putting forward a new model for developing new anti-cancer treatments that addresses the needs of patients and society. *Molecular Oncology* 13:558–66. The figure is republished under the terms of the Creative Commons Attribution License

done. A well-known case was intensive chemotherapy with autologous stem cell transplantation for breast cancer, which was shown to have increased toxicity with no greater survival, but only after many thousands of women had received it.

Another example was a strategy for managing advanced ovarian cancer with platinum-based drugs, adopted in the late 1990s. Thanks to an independent validation trial published in 2017, oncologists now know that a protocol administered as a standard of care to many women did not extend overall survival, had significantly shorter progression-free survival and scored worse in quality of life.

The role of such applied research extends widely in oncology, and not only to new agents, but the worry is that, as the latest treatments enter use, they too may be found in the end to have been suboptimal.

Building consensus on the way forward

Since publishing the manifesto, the EORTC and STOA have engaged with stakeholders such as health technology agencies (HTAs), regulators, clinicians and patient advocates on how this could work.

A survey by STOA asks questions such as:

- How should such research be financed?
- Could it run in parallel with classical registrational trials, or only after marketing authorisation?
- How would regulatory agencies use the data?

Interviewees were asked about the current situation, what the features of treatment optimisation studies could be, and how they could be accepted.

Reporting on the findings of the survey, Lacombe and colleagues describe the dominance of drug-centred registrational trials that are not primarily designed to inform clinical practice and do not provide the information doctors and patients need. The report also makes reference to studies showing that, several years after getting market access, a majority of oncology drugs approved in the US and Europe had no or insignificant evidence of impact on survival. A second stage of trials after approval, if done at all, are usually not pre-planned and involve different actors, with industry rarely interested. Hence the need for a formal programme of pragmatic trials.

Most respondents to the survey agree that current drug development is not sufficiently patient-centred, and that there is insufficient real-world evidence, which 'severely complicates' the decision-making of HTA bodies, payers and clinicians. They agree that studies are needed that have fewer inclusion and exclusion criteria than the classical clinical trial, and employ the standard of care or the best available alternative treatments as comparators.

There is no such consensus on the optimal timing of studies, however, nor on whether such trials would need to be randomised.

Importantly, the survey showed broad backing for regulatory measures to support treatment optimisation. Views on who should fund treatment optimisation studies were largely split between the option of funding by academic and non-profit organisations or by consortiums of all stakeholders. A combination of public and private funding is seen as most feasible.

Asked for pluses and minuses, respondents mention, on the plus side, the use of clinically relevant outcome measures, cost savings, rewarding treatments that add clinical value, and more accurate prediction of real world side-effects. But there are questions about who will foot the bill, the lack of a framework for such studies, reluctance of clinicians and industry to take part, and potential ethical and legal issues.

Three policy options for how treatment optimisation studies could fit within existing regulatory pathways are on the table:

- Making treatment optimisation studies part of the requirements that manufacturers have to satisfy to obtain a marketing authorisation
- Including such studies as part of industry's post-authorisation commitments
- Using conditional reimbursement mechanisms to compel makers to carry out treatment optimisation studies.

Regulatory perspective

In March 2020, the European Medicines Agency (EMA) published its regulatory science strategy for the next five years. The document addresses many of the challenges that are raised in the EORTC manifesto and work of the STOA panel. Guido Rasi, the EMA's executive director, accepts that cutting edge treatments such as CAR-T cell therapy raise fundamental questions about how they are assessed and valued. Speaking at the STOA event, Rasi mentioned the concept of 'evidence by design', recognising that new types of studies need to be planned, and requirements for

Rasi envisages a new role for regulators 'at the crossroads between science and healthcare systems'

post-licensing evidence generation specified, such as what data is collected by cancer registries. Rasi said he envisages a 'rolling review' of evidence revision, and essentially a new role for regulators 'at the crossroads between science and healthcare systems', acting as a 'catalyst' to enable translational research that fits into the reality of healthcare systems.

The new strategy puts forward a lot of initiatives, and indicates a willingness to engage with the clinical optimisation agenda, but as yet has few hard facts. Among the promises are:

- Developing a methodology to incorporate clinical care data sources into regulatory decision-making
- Providing guidance on the roles of patient preferences in therapeutic contexts and regulatory decisions
- Ensuring the evidence needed by HTAs and payers is incorporated early in drug development plans, including requirements for post-licensing evidence generation.

The strategy also calls for the EMA to pilot a system for rapid analysis of real-world data (including electronic health records) to support decision-making at the EMA's authorisation and risk committees, and generally there is much emphasis on this tier of evidence at European level. While real-world data can include pragmatic trials, projects such as the European Health Data and Evidence Network (EHDEN), launched at the end of 2018 within the Innovative Medicines Initiative (IMI), aims to harmonise 100 million, anonymised health records across multiple data sources, and ties in with other IMI projects such as Big Data for Better Outcomes (BD4BO). (See also the EU Horizon 2020 project, HTx – this has funding of close to €10 million and aims to resolve the effectiveness of complex treatments at HTA level.)

Indeed, a paper by authors from the EMA and other agencies puts forward the idea of a 'learning healthcare system', based on electronic health records and other routinely collected data – which in oncology will be the "only hope" to get to grips with the complexities of combinatorial therapeutic strategies, they argue (Eichler H-G et al. *Clin Pharmacol Ther* 2019). See also a recent paper on new analytic methods using real world data and also cross-trial data from completed randomised trials (Eichler H-G et al. *Clin Pharmacol Ther* 2020).

Can Europe lead the way?

Pressure to give timely guidelines to oncologists faced with many new agents is only going to increase, as was well articulated by Maurie Markman from Cancer Treatment Centers of America in Philadelphia, in a short MedScape piece, Defining standard of care in oncology (medscape.com/viewarticle/930078).

Focusing on his own speciality of ovarian cancer, he says that platinum-based therapy was unchanged for many years, but a number of new options including angiogenesis inhibitors and PARP inhibitors have recently become available. What is the optimal strategy among these different agents? Will there be trials that compare one strategy to another or even several strategies to each other? This falls into the pragmatic trials arena, he adds, but there is no simple answer to defining optimal patient management – the standard of care – when 'very exciting' strategies are entering the scene on an almost daily basis.

Lacombe considers that the sheer unsustainability of the current system – its huge costs and waste – will force change. He does not pretend to have all the answers, which is why the EORTC brought the multistakeholder treatment optimisation initiative to the European Parliament. But proposing what amounts to a big and potentially very costly new tier of research, and extensive collaboration around Europe on both research and data collection, will need a lot of discussion.

A steer has come from EU health ministers, who have been briefed on improving evidence of patient benefit, and increasing information exchange between regulators and national authorities, and have said that convergence is in the interests of EU citizens. And in that lies the challenge of the European project itself – with the UK now gone, the opportunity for Europe to lead the world in this and other aspects of technology may be getting harder to achieve, but nowhere else globally is likely to have both the capacity and the political will to attempt such a mission.

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How retractions are helping cancer research

Retraction Watch was born as a blog to unveil the reasons behind the retraction of a paper. It is now a comprehensive database helping to foster a better quality of research, including in oncology. **Esther Paniagua** talked to science journalist Ivan Oransky, one of its founders.

In 2015, cancer researcher Anil Potti – back then associated with Duke University in Durham, North Carolina – was found guilty of research misconduct by a US federal investigation led by the Office for Research Integrity of the Department of Health and Human Services. "The findings bring to a close one of the most egregious US scientific misconduct cases in recent years" commented *Science* magazine (sciencemag.org, 9 November 2015) .

The episodes of misconduct listed by the Office for Research Integrity included faking research data in research reports from six different NIH grants, swelling the number of patients involved, altering scan results and data sets, and reporting predictors and/or their validation by disregarding accepted scientific methodology. In all, false data were reported in eleven now-retracted papers, as Ivan Oransky – science journalist and research integrity watchdog – reported in *Retraction Watch*, a blog that he and his colleague Adam Marcus had launched with no clear plan – "We had a lot of good stories" he says in an interview with *Cancer World*.

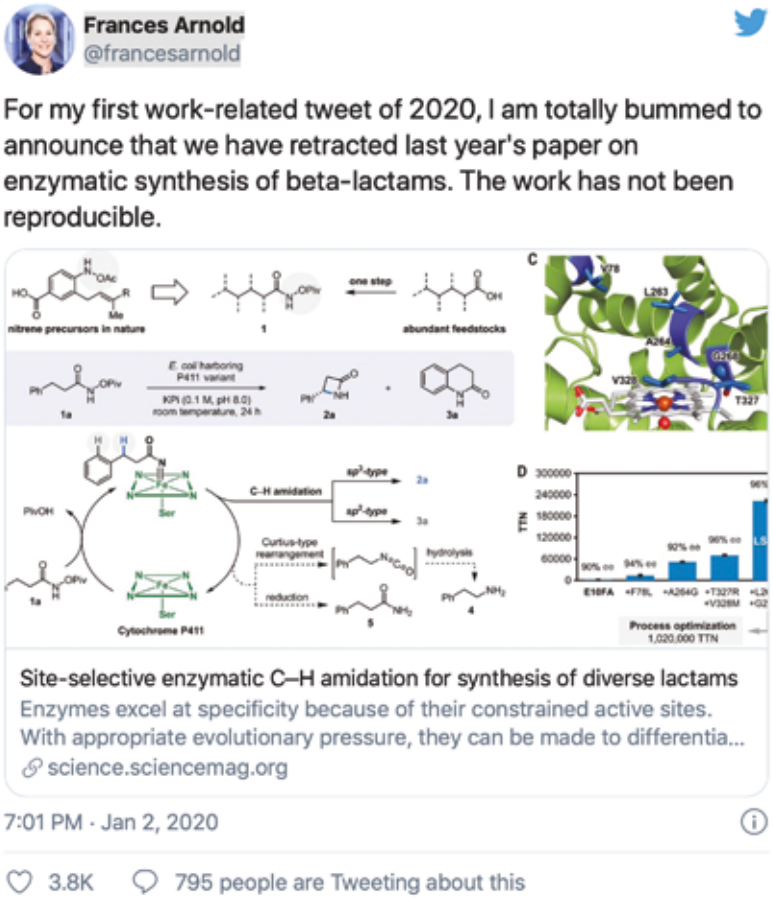
Today, *Retraction Watch* is much more than a blog. Launched and updated as a passtime, it has become

a freely available, comprehensive database detailing nearly 21,000 retractions, "compared to just over half that on sites like Scopus," says Oransky. "Nothing like this exists because no one has been cataloguing retractions so effectively."

Not a death penalty, but...

An article in *Science* magazine (sciencemag.org, 25 October 2018) highlighted the stigma attached to retraction, referring to it as 'science publishing's death penalty'. "Because a retraction is often considered an indication of wrongdoing, many researchers are understandably sensitive when one of their papers is questioned," wrote the authors. They pointed out that such stigma could be counterproductive, potentially "leading to practices that undermine efforts to protect the integrity of the scientific literature." Stigma can be a problem for those who want to invite scientists to actively suggest a retraction when they realise that something has gone wrong with their work.

"Negative retraction stigmatization has mainly been borne by authors, whereas journals and publishers, except for headline-grabbing reports, have thus far largely avoided this stigma," writes Jaime Teixeira da Silva in a paper published in *Research Ethics* on April 2019 (doi/10.1177/1747016118802970). "One of the efforts to destigmatize retractions, at least those for honest errors, has been to try to relabel or rebrand retractions. The terms 'self-retraction', 'amendment', 'publisher-caused error', and others have emerged, but such a diverse lexicon may complicate the publishing landscape more than it resolves the stigma," said da Silva. "Seeking euphemistic terms to represent a truth within a toxic context of negative stigmatization only politicizes the issue, and does not resolve it. A change is needed in the culture within the biomedical community, to acceptance of critique, and the culture of shaming needs to be halted in order to achieve this. Only then can academics assume greater responsibility, without the risk of being shamed, of retracting their faulty literature, 'honestly', when they feel that this is needed."



Oransky has now become an expert in this peculiar field of research, and was initially driven by curiosity: "There are a lot of hidden stories, just sitting out there, and not being paid attention." The other factor that attracted his interest is that the short texts accompanying retractions are "often very unclear or actually wrong". That's why at some point he decided to invite his students of science journalism at Columbia University to collect as many details as possible on each cryptic retraction notice: "There was a transparency problem. No one likes to admit mistakes," he argues.

Cancer kills, bad science does too

Why should oncology researchers, cancer practitioners, and patients know more about retractions? "People have the right to know, because it can affect not

Cancer research that smelled fishy

A recent retraction (January 2020) regards a paper on non-small cell lung carcinoma (NSCLC) published in 2015 in *Human Immunology*. After studying 18 healthy controls and 66 untreated patients with NSCLC, researchers claimed to have found a subset of cells that "might play an important role in the clinical progression of NSCLC." However, "serious problems with copied and re-labelled images in several figures" were found, as the editor-in-chief of the journal explains in the retraction notice. "This strongly suggests that the data was manipulated. The authors were unable to provide the raw data files to prove otherwise. This makes the overall conclusions of the paper unreliable and violates our ethical publishing policies," he adds.

Ethical violations compromised the integrity of a paper on brain cancer published in October 2019 in *PLOS ONE*. The original paper was published in January 2013. The authors said they had been able to identify a way to suppress cell growth and invasion as well as inducing apoptosis. Their study revealed, "for the first time" two kinds of receptors in the Notch cell signalling system supposedly playing different roles in the biological processes of astrocytic gliomas. But the retraction notice raised concerns "about several results reported in this article," including issues about data, image duplications and ethical violations by the authors.

An unreliable paper on glioblastoma was published in *ACS Biomaterials Science & Engineering* in May 2018. The authors address "glioma stem cells (GSC) as a critical therapeutic challenge for glioblastoma". But the validity of one of the images was questioned – as the retraction notice explains – and with that the results of the study.

Data concerns also led to retraction of a research paper on acute myeloid leukaemia, published in May 2018 in *Haematologica*. The authors claimed to have found, on patient-derived mouse xenograft models, a key target for the survival of acute myeloid leukaemic stem cells, and a way to inhibit it in patients with a specific mutation (FLT3-ITD+), related to a particularly poor prognosis. They also recommended including the inhibitors in the treatment regime for that kind of acute myeloid leukaemia.

In the retraction notice, the authors recognised that there was something wrong with the data and images prepared by the first author of the article, but accepted to share the same fate: "While we believe the overall conclusions of our manuscript remain intact, the most appropriate course of action is to retract the paper. All authors have agreed to this retraction. We deeply regret this circumstance and apologize to the scientific community for the inconvenience that this may have caused."

only science but also patient care. If researchers are committing misconduct or fraud, taxpayers and patients who are participating in related clinical trials have to be aware of that. Most papers that should be retracted are not. This is not merely an academic issue, it affects patients," Oransky explains.

Of course in an academic world dominated by the 'publish or perish' mantra, in which every published paper might contribute to professional success, for many researchers a challenge to one of their papers could pose a threat to their career.

In fact, retractions should be seen as a good thing, says Oransky. "It's actually proven that you become more trustworthy if you do that." Contrary to what might be expected, he says, "actually nothing bad is likely to happen when you retract a paper for an honest error and are clear about that."

When the Nobel laureate said "Oops"

After many years of caution, some researchers are now moving to this proactive approach: "For my first work-related tweet of 2020, I am totally bummed to announce that we have retracted last year's paper on enzymatic synthesis of beta-lactams. The work has not been reproducible." This candid confession was published on Twitter on January 2, 2020, by Frances Arnold, who was awarded the Nobel Prize in Chemistry in 2018.

The reaction in the twittersphere was overwhelmingly positive: "You should not be bummed but just proud for taking action. Thank you for keeping the literature records accurate," summed up one of the comments. "Thank you for providing a role model for scientific integrity! It's so scary to be honest, seeing inspiring people lead the way in honesty helps me stay strong when I need to," said another scientist.

When it comes to cancer research, failure to take prompt action on questionable research can have

repercussions for treatments administered, as happened when a paper on CAR T cell therapy (Samaha H et al. *Nature* 2018) was retracted in early 2019, after many clinicians had started to feel excited about it. It was a mouse study about a system targeting therapeutic T-cells to brain cancer, showing a new way to deliver CAR T cells across the blood–brain barrier.

From *Nature* to the *New England Journal of Medicine*

"A multi-institution international team led by researchers at Baylor College of Medicine has developed a new strategy to overcome one of the main obstacles in the treatment of brain cancer – access to the tumour," read the press release, published in September 2018, that promoted the results in the popular media. According to the retraction notice, the paper had issues with figure presentation and underlying data, and the authors couldn't confirm the results.

Setting the record straight in *Nature* magazine was not enough, in this case, since the unreliable paper had, in the interim, been included in a review that appeared in the *New England Journal of Medicine*. The review had to be retracted as well, so as not to contribute to further misinformation. There is no way to know how many researchers and clinicians read about the study and then missed the news of the retraction.

Research on osteosarcoma, the most frequent primary bone tumour in children and adolescents, was also affected, with a paper published in April 2018 being retracted in February 2019. The authors claimed that their research with a mouse xenograft tumour model confirmed the discovery of a new inhibitor of proliferation, migration and invasion of human osteosarcoma cells, called A005, which they claimed had stopped tumour growth and prevented osteosarcoma-associated osteolysis. "These findings indicated that A005 may be a promising candidate drug for the treatment of human osteosarcoma," the now retracted paper said.

The reasons for the retraction were concerns about data and duplication of images that led to unreliable results. "The results and conclusions of the study cannot be confirmed, and the authors wish to withdraw the paper completely so as to correct the publication record," the retraction note says.

Speak now, or forever risk your reputation

Sometimes retractions are caused by minor problems that may not appear to compromise the validity of conclusions. In this case patients are less likely to be affected. Still, the impact on researchers' reputations can be significant if they have not been proactively forthcoming about the mistakes. This was the case with Carlos López-Otín, a prestigious Spanish researcher who insisted that he was the subject of a witch-hunt after eight of his papers were withdrawn from the *Journal of Biological Chemistry*.

The papers – published between 2000 and 2007 – related to the identification of new human genes involved in cancer or other diseases. The retractions related to manipulation or duplication of images, or the reuse of experiments reported in previous papers. Similar problems led to a later self-retraction of a study published in *Nature Cell Biology* a few days after the journal had expressed concern. A few months later, *Nature* withdrew a 2017 mentoring prize it had awarded to Carlos López-Otín.

There is no way to know how many researchers and clinicians read about the study and then missed the news of the retraction

López-Otín and the other authors of the paper argue that the reasons for the retractions are "very minor" formal errors, and that other independent groups have validated their results afterwards, as reported in an article in the Spanish daily *El País* (28 January 2019).

A systematic database of retractions is in the making

In 2019 *Retraction Watch* documented 36 retractions in oncology: "We have about 1,500 retractions per year out of about two million papers in total," Oransky says. "If you visit PubMed, Medline, the web of *Science* or Scopus, you can search for retractions, but their archives are not systematic and a lot of what you find is actually many false-positives. Also, not everything is in any of them," he says.

The systematic work that led to the database constantly updated by *Retraction Watch* was made possible by a substantial grant offered by a private foundation, and of course by the endless curiosity that pushes Oransky and his colleagues to ask annoying questions: "We have to question what we read, to be able to trust what we read."

Sharing Progress in Cancer Care (SPCC) pursues the promotion, coordination and implementation of programmes, projects and initiatives in the field of cancer education, with particular emphasis on scientific progress and innovation in the Cancer Care Continuum.

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Stella Kyriakides

EU Commissioner for Health

When Stella Kyriakides took on the post of EU Health Commissioner in September 2019, Europe's cancer community knew they could trust her to fight their cause. Within months she was launching a public consultation on Europe's Beating Cancer Plan. Then came COVID. **Alberto Costa** asked her how her experience as a breast cancer survivor and patient advocate shaped her approach to her new role and how she is coping with the demands of responding to a major public health crisis while still delivering on the expectations of the cancer community.

Cancer World: *You were still becoming familiar with your new office at the Berlaymont in Brussels when the COVID-19 pandemic exploded. How did you respond?*

Stella Kyriakides: In Greek, there is a saying: "In difficult situations, you just roll up your sleeves and get the work done." There was no option but to do everything to rise to the challenge of the greatest public health crisis in memory. Quickly getting a grasp of the issues at hand, ensuring we have the right expertise in place, connecting the dots to our Member States and European Parliament, and finding pragmatic, concrete and workable solutions as quickly as possible in a calm and effective way. The COVID-19 crisis has affected the lives of countless citizens and businesses around the globe. As European Commissioner for Health and Food Safety, it is my responsibility to ensure that we do everything we can to protect public health. It is important to be prepared for any eventuality at all times, and be ready to react swiftly. We have faced countless challenges since the beginning of the pandemic. However, these challenges and difficulties cannot in any way be compared to those faced on a daily basis by frontline workers. Despite unprecedented pressure, and in the most difficult of circumstances, they continue to provide lifesaving treatment and care to thousands of citizens, and to put themselves at risk every day to protect us all. They are the true heroes of the COVID era. Clapping for the carers night after night was one of the many inspiring acts of solidarity we witnessed across Europe during this crisis.

CW: *You've been a Member of Parliament for many years in your home country, Cyprus, where problems have relatively limited dimensions. How does it feel to now have such a huge responsibility at a European level?*

SK: It is of course a great responsibility, but I have always approached every personal challenge in a similar way: setting high targets, working hard and giving

my best to deliver on expectations. This means, among other things, to be able to work in effective teams, in a coordinated and focused way, taking all viewpoints on board, having flexibility when needed to find solutions – much more so when we find ourselves in unprecedented crisis situations.

This tragedy we are experiencing in Europe and the world has had an immeasurable cost, primarily on human lives, but also on our economies, on society at large and, unfortunately, much more on those most vulnerable amongst us.

CW: *Europe's cancer community is expecting great things from your Beating Cancer Plan. What are you trying to achieve with it and how?*

SK: Every year, 3.5 million people in the EU are diagnosed with cancer, and 1.3 million die from it. Many of us have personal experiences and know the pain it causes for those we love. This is why the high expectations that you mention are justified and why Europe's Beating Cancer Plan is a major priority for myself and for the whole von der Leyen Commission. Our aim is to reduce the cancer burden for patients, their families and health systems, focusing on: prevention through healthier lifestyles; improved screening and early detection; and equal access to medicines and innovative treatments. With this focus, we are aiming to achieve a better quality of life for cancer patients, for those living with advanced disease, for survivors and carers. In recent months, we have also seen how the COVID-19 pandemic has affected cancer prevention and care, underlining the importance of robust and resilient health systems that function in all circumstances. Europe has been actively working to fight cancer for decades. We are committed to presenting the Europe Beating Cancer Plan by the end of this year. This could not be more personal for me – as it is also for so many of us.

CW: *As a pioneer of cancer patient advocacy, you gave time and energy to Europa Donna and to the breast cancer world. What does this bring to your role as Health Commissioner?*

SK: Being a breast cancer patient and patient advocate has been part of my journey in the area of health for over twenty years. This could not but influence my life in the public sphere from my time as a parliamentarian in Cyprus and now as European Commissioner. I firmly believe patients need to have a central seat at the table when decisions about them are made, because their voices need to be heard. Equally, I have learned that we all need to work together with all stakeholders to bring about change. This means bringing together patients, scientists, decision makers, industry, etc. This is the only way we can bring change. That has always been my belief as an advocate and it continues to be my compass now in my role as Commissioner.

CW: *Most politicians are men. Do you as a woman struggle more than your male colleagues to combine your political position with your personal and family life?*

SK: Equality is a founding principle of the EU and an integral part of our Charter of Fundamental Rights. I am very proud to be part of the first European Commission led by a woman, in the most gender-balanced Commission College we have ever had. On a personal note, I was lucky with the fact that I had supportive parents, and a supportive husband and children, so my gender was not limiting. But many women in the world are not so fortunate, and I have been witness to this discrimination – it is for these women that we must act. Gender equality requires political will and political vision. And it requires us all to be the strongest advocates for gender equality. This is a cause I have championed in the past, and which I will continue to champion for as long as I am in public life.

Stella Kyriakides is Cypriot politician who was appointed European Commissioner for Health and Food Safety in 2019. She has represented the Nicosia district in the Cypriot national parliament since 2006, and represented Cyprus at the Parliamentary Assembly of the Council of Europe (PACE) between 2012 and 2019, serving as president of PACE in 2018–2019. Her professional training and early career was in the field of clinical psychology. After being diagnosed with breast cancer she got involved in cancer patient advocacy, serving as president of Europa Donna, the European Breast Cancer Coalition, between 2004 and 2006. She has consistently championed the cause of cancer patients and survivors throughout her political career.

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