# Emiel Rutgers:

## a surgeon for the genomic era

Marc Beishon

Emiel Rutgers was 'tailoring' his therapies long before the term was popularised. He pioneered breast conservation and neo-adjuvant chemotherapy in the Netherlands against opposition, but was also an advocate, just as controversially, of complete mastectomy of healthy breasts as an option for women at high risk. To be effective in this genomic era, cancer surgeons must keep abreast of the science, he argues.

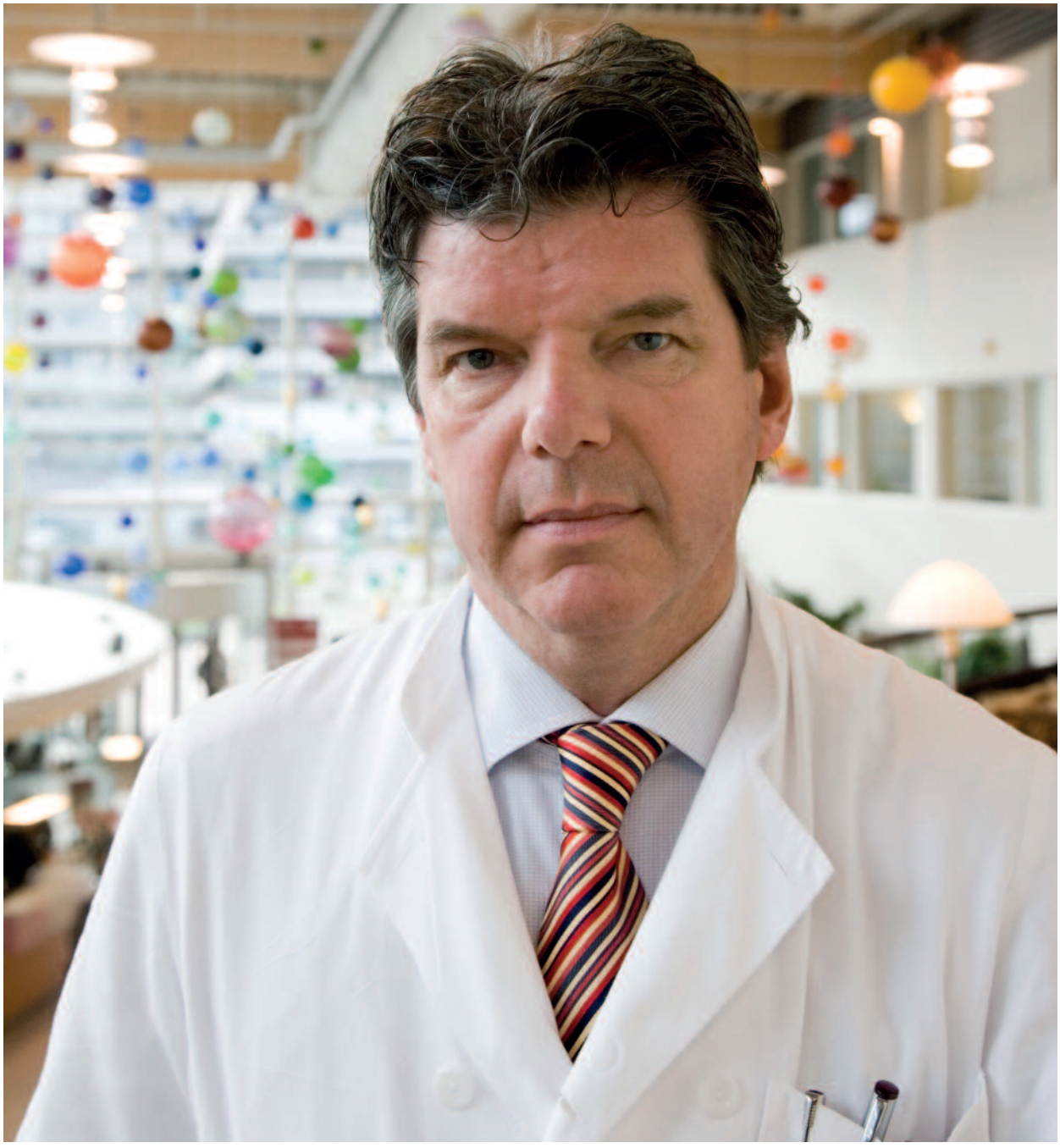
Breast cancer has attracted – and continues to attract – some of the most talented and often outspoken oncologists the world over. That is perhaps not surprising, given the emotional context of the disease, and the controversies, breakthroughs and advocacy surrounding issues from screening to managing genetic risk, new targeted therapies and breast conserving surgery. Surgeons such as the breast conserving pioneers, Bernie Fisher and Umberto Veronesi, and the anti-screening Michael Baum in the UK, have been at the forefront of many of these debates.

Emiel Rutgers, head of surgery at the Amsterdam Cancer Institute (NKI), and professor of surgical oncology at the University of Amsterdam, is a man cast in a similar mould, both tireless and outspoken in arguing his case on how to improve breast cancer research and treatment. An oncologist who started out in the 1980s, he has been involved in most major battles against the orthodoxies of the time, especially proving the case for breast conserving surgery, preventive mastectomy, neoadjuvant therapy and sentinel node biopsy.

But as a physician now straddling the older and younger generations – he is in his early 50s – he's also in the vanguard of movements to define and establish what he sees as true multidisciplinary working, including breaking down for good at national and international levels the boundaries between the oncology disciplines, shaping modern surgical oncology training and – very significantly in his view – the drive to bring key biomarkers and especially prognostic and predictive genetic testing of tumours into widespread clinical use.

"My ideal – and aim – is to tailor our interventions for primary breast cancer with a complete readout of a tumour's propensity to disseminate around the body. We will also be able to include genetic inheritance and so know the peculiarities of both the individual and the tumour. I'm optimistic this will be in place in the next five to ten years – but I find it very hard to wait."

Breast cancer surgeons, he adds, have every reason to be at the forefront of targeted therapy. "I prefer in any case to be seen as an oncologist specialising in the surgical part of the discipline. But as the surgeon you are the first to start treatment in



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many patients, and you have to perform a very intimate act. You have to look her in the eyes and gain her trust for the proposed treatment, and that can include chemo- and radiotherapy, the results of the pathology report and so on. If you just say, 'This is a high-risk cancer – go and see the medical oncologist,' you jeopardise your relationship with her. You need the knowledge to follow and guide the patient throughout her care."

Rutgers has more knowledge about how to approach breast cancer than many oncologists, combining as he does the latest surgical techniques

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with all the surrounding biological, radiation, drug and quality-of-life issues. While he is a lead author of many papers and guidelines on surgery, working for example with EUSOMA (the European Society of Mastology), he is also one of the principal investigators in the much discussed MINDACT trial, researching the prognostic and predictive value of a breast cancer gene signature, and of AMAROS, another large international trial that is looking at eliminating lymph node removal by using the sentinel node procedure and radiotherapy instead.

Having chaired the European Breast Cancer Conference in Berlin last year, and ever present at all the main meetings, he has become a key figure in international collaboration as well as an ambassador for the Netherlands' breast cancer effort. At the NKI, he leads a relatively small team of 10 surgeons who operate on most of the cancers bar brain tumours, but the centre sees 13,000 patients annually and has a track record in clinical innovation and effective working that has resulted, for example, in some of the lowest relapse rates after breast conservation, despite having a less favourable case mix than other hospitals in the region.

At the time of this interview, Rutgers had just returned from the San Antonio Breast Cancer Symposium and, in typical style, he mentions among the highlights two studies that are not directly about surgery. One is a small but very significant study demonstrating a very interesting biological response to preoperative short-course single-drug therapy involving lapatinib (Tyverb) in a majority of HER2-positive breast cancers; the other is on the use of bisphosphonates, which can not only improve quality of life by preventing bone fractures but may also improve survival.

As he says, "Twenty years ago there were some medical oncologists who were saying chemotherapy would eradicate surgeons – but surgery is still the mainstay of optimal local treatment." However, fast-tracking any effective new treatment across the cancer life course has to be the goal of any oncologist, and no surgeon, he feels, will be effective unless they remain fully up-to-date on what it means to operate in the genomic era.

Rutgers was always going to be a surgeon – he even found a drawing of his at his parents' house done aged around nine, showing him doing an operation. "I was attracted by heart surgery – impressed by the then gods of the field such as Christian Barnard. But later I thought it would be too dull – I didn't want to be doing coronary bypasses for the next 30 years." After brief thoughts of switching to psychiatry, he embarked on general surgery training at a hospital in Eindhoven, under the wing of Huub Kluck, who introduced him to surgical oncology and breast cancer in particular, and Rutgers became a proficient thoracic and breast surgeon.

"But breast surgery then was just mastectomy and I wasn't happy – I thought I'd done a neat job, but three years later women had died. It was the very early days of breast conservation and adjuvant treatment, and Kluck was convinced we didn't need to take the whole breast away – but that was against all the odds here in the Netherlands."

Surgeons in France, in particular, were leaders in implementing breast conservation, and several were invited to demonstrate the technique in Eindhoven. Meanwhile, Rutgers had been introduced to one of the Netherlands' top cancer specialists, Emil van Slooten at the NKI, under whom he did a PhD on the follow-up of women treated for breast cancer, at the University of Amsterdam. "Kluck had introduced a good follow-up programme that included psychological aspects at Eindhoven," he says, and Rutgers was set firmly on course to be the rounded oncologist he is today.

After a year's fellowship at the NKI, a permanent post for a surgeon opened up there and Rutgers has worked his way up to his present position over the last 20 years. He was of course immediately involved with developing breast conservation work, and it was his colleagues at the NKI, Joop van Dongen and Harry Bartelink, who started the EORTC

(European Organisation for Research and Treatment of Cancer) randomised trial of conservation versus mastectomy. Rutgers was also instrumental in helping to introduce the sentinel node procedure into the clinic and later to refine it; he helped develop the field of oncoplastic surgery to improve cosmetic outcomes; and he started a family cancer clinic for treating high-risk groups. His work on lung and other cancers was gradually phased out.

In breast, other more recent highlights have been the use of neoadjuvant therapy (chemotherapy before surgery), and the microarray gene profiling technique – the NKI is a leading centre in the MINDACT trial, and set up the biotech spin-off Agendia to market the MammaPrint tool.

He describes much battling against vested interests in progressing some of these areas. "Early on, I established the high-risk family clinic, even before we knew about the BRCA 1 and 2 genes, and offered preventive surgery. But back then most doctors were ignoring the needs of women who felt they were at high risk. I remember once over dinner my sister-in-law being horrified about taking away a healthy breast – but she understands now."

Rutgers brought in a psychologist to talk through the issues properly with women and their partners, but he notes, "While the discovery of BRCA1/2 has made such work easier, it has also made it more difficult where we know something is wrong but we can't find it. Eventually, we will have gene maps that reveal levels of risk, but we'll never have other genes with the same level of high risk we get with BRCA, and the problem is that women will often perceive their risk as higher than it actually is."

MRI screening is now standard for women at high risk at the NKI, he adds, but presents its own issues. "For BRCA 1, where cancers grow very fast, I'm unsure of the interval, as having an MRI, say, every six months for 20–30 years – with the inevitable false positives – is no way to live."

He is struck by the impact of hormones on breast cancer risk. "I visited Chile, which has a population of about 16 million, about the same as the Netherlands, but we have three times the number of breast cancers. The age profile of the two countries is similar, but women in Chile have a first child on average at age 25, while our average age is 31." All told, he considers that a woman who starts menstruation in the mid-teens, has an early child and breastfeeds, and then has an early menopause has one-third of the risk of women who undergo many more menstrual cycles.

For women electing for preventive mastectomy, Rutgers warns that it is an all-or-nothing procedure. "We do our utmost to remove all breast tissue and we have found that, of the hundreds we have done, no women have breast cancer at follow-up and we can say goodbye to them. But if you leave some tissue behind – as some surgeons agree to do elsewhere for cosmetic reasons – one study shows there will be a small number of cancers after 10 years. But women in their 30s have a life expectancy of 50 years and there could be many more to come."

It is one reason that Rutgers and colleagues have formed close relationships with plastic surgeons to improve cosmetic outcomes, and he adds that this is becoming more and more important now that increasing numbers of breast cancer survivors are living long lives after mastectomy or breast-conserving procedures. "I much prefer plastic surgeons to do reconstructions – you wouldn't ask them to remove tumours, which is what surgical oncologists need to focus on. The Americans told us for years you could just leave the tissue open and close the skin, but after five years the cosmetic outcomes are often a disaster." (For more on this, see *New oncoplastic techniques can avoid mastectomy*, page 13.)

While mastery of the surgical aspects of breast cancer are of course critical to the best outcomes, the emphasis of Rutgers' work has increasingly been on following, leading and implementing all aspects of targeted therapy. Breast conserving work was the start, and he has since become an authority on the sentinel node procedure, which has become one of the most reliable methods of assessing axillary lymph node involvement – and where he is pushing the

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boundaries. "What we do differently here is also chase and remove lymph nodes outside the axilla if we see them on scans, such as in the internal mammary chain, that were ignored in the past, and that's not common. It's an old but reliable law – the better the staging the better you can adjust the treatment and the better outcomes will be."

Not that he can prove it improves survival, as the incidence of positive nodes outside the axilla is relatively low and no trial could be designed to test the difference that obtaining this information would make – it is more about Rutgers' drive to obtain as much biological data about tumour behaviour as possible. And crucially, there is a misconception among some patients and doctors that the lymph nodes are the primary filter for harmful dissemination of cancer cells. "That is nonsense of course – node-negative patients have millions of tumour cells circulating in the bloodstream – I can think of patients with node-negative disease who have far worse prognoses than women with, let's say, four positive lymph nodes. It is the propensity of tumour cells to disseminate that is the target, not the lymph nodes."

This is why Rutgers has become so involved – and impressed – with the MINDACT trial and the application of the MammaPrint test in the clinic. "The key issue is that the gene array predicts much better the propensity of cancer cells to spread and 'take' in other sites in the body – we have to find better prognostic factors than the subjective ones we use now, such as tumour size, grade and nodal involvement, and I have no doubt we will be able to change cancer management substantially."

Good news about MammaPrint keeps on coming, he says. The MINDACT trial now looks at node-positive as well as node-negative cancers, and may prove that 40% of node-positive women will not need chemotherapy, only hormonal treatment. "This is for women with one to three positive nodes – and in places such as the US physicians would say they'd go to jail if they didn't treat all of them with chemotherapy." Other news concerns determining better how to treat younger women with small tumours, and a 'huge difference' in predicting chemotherapy outcomes for low- and high-risk hormone-responsive tumours, whereas the existing consensus (such as from the St Gallen conference) is not nearly so clear.

Rutgers stresses that he has no financial involvement with Agendia, the biotech spin off from the NKI that has developed MammaPrint and other gene profiling tests. "But I'm certain that if it had not been set up, the test would not be available so quickly. The developers of the gene signature in Rotterdam for breast cancer, which does the same thing I'm sure, have not yet found a company that will take it to the market."

As a vivid example of the value of the test, he cites one of his patients. "She was a 36-year-old woman, pregnant with her third child, and found a lump at 10 weeks into the pregnancy, which was invasive cancer. She decided to have a mastectomy, skin sparing with reconstruction, and a sentinel node procedure. The cancer was a 15 mm grade 2, oestrogen-positive, HER2-negative tumour which, according to existing guidelines, means adjuvant chemotherapy. We had the tumour frozen and ordered a MammaPrint test, which showed it was low risk, and the woman chose not to go for chemotherapy, kept the baby and had hormone treatment once she'd delivered. This is one of many examples now."

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MammaPrint he notes, not from surgeons but from medical oncologists and radiotherapists afraid of losing part of their practice, and worried, too, that they might miss one patient out of a hundred by omitting chemotherapy. There is also, he adds, a bias in the ASCO (American Society of Clinical Oncology) guidelines that favours a competing American test, Oncotype DX, which is partly due to the lack of an international presence on the committee, feels Rutgers. "But the fact that MINDACT is supported by drug giants Novartis, Aventis and Roche shows that they recognise that we cannot use endless chemotherapy and can only afford so much."

He cannot emphasise more the importance of the surgeon working with a pathologist to collect fresh tumour samples and freeze them to preserve the RNA for use in tests such as MammaPrint. "I go almost as far as saying it is criminal not to do so – it is life insurance for the patient, as 20% of them will have a recurrence despite what we do at present. There are more than 50 new targeted drugs around now, and we will only have a chance of success if we have the right targets. It's the only way we can keep breast cancer treatment affordable. But if you do not collect fresh samples you cannot go back to the primary tumour five years later when a woman comes back with metastatic disease. We are a fairly small academic-style hospital with 150 beds – and if we can keep a fresh-frozen tumour bank, certainly all the other major centres must be able to do so."

Another controversial area he mentions is neoadjuvant therapy, used to shrink tumours before surgery. "If you know you will be giving chemotherapy later, why not start with it? I have pressed for this against much opposition." One advantage includes shrinking the tumour for better breast conservation. "We can do that safely on 40% of patients who would have been scheduled for a mastectomy – and as you can see the tumour, if it doesn't work you can change to another therapy." He adds that in 20% of cases the tumour disappears completely and for certain subgroups that rate rises to 60%. "If you achieve that result, a woman's chances are very good, with five-year survival rates well above 90%. Neoadjuvant therapy is a great avenue and patients like it because they can see how chemotherapy actually makes the tumour

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smaller, whereas with adjuvant therapy there is much more uncertainty about whether it works."

Naturally, missing the chance to work fast to remove a tumour is controversial, while medical oncologists and radiotherapists find it more difficult to formulate later treatment. "Surgeons don't like it – they ask, 'What should I do? How much should I take away?' But it is about doing a good breast conserving job as usual."

All this knowledge, however, can only be put into practice in a fully functioning breast unit, and Rutgers' blueprint for an ideal facility is certainly demanding. "It's not just a plate on the door. You need to have everything in place for every possible diagnostic and treatment possibility, with the right multidisciplinary team and the right hardware, including digital mammography, image-directed biopsy, ultrasound and a dedicated breast MRI – and all the treatment modalities. All the team should be largely dedicated to breast cancer." He is a firm proponent of mammography screening as a 'pillar of the breast cancer care house'.

Many units fall down by organising around the needs of the physicians and not the patient, he feels. "A common problem is the ego of doctors, especially surgeons, who want to keep control of everything. But it is not necessary – they can devolve much responsibility to other team members such as nurse practitioners. A particular issue that concerns me is where patients are booked in and out for several diagnostic procedures that could be done the same day. It is a nonsense only doing certain things at set times of the week – it leads to multiple appointments and reports and potential for miscommunication, as well as a lot of wasted time – and especially inconvenience and stress for patients. You want one file, one fast friendly track for the patients and for everyone to speak the same language." And developing a complete, streamlined diagnostic approach, he adds, can be a shortcoming in even some of the larger breast units around Europe, even if subsequent care is first rate.

The most important outcome of all, Rutgers says, is a more satisfied and reassured patient. "My strong feeling is that well-informed patients who trust the treatment team from the start have the quickest and least complicated recovery, as they sense they are being taken care of." He mentions a study he helped design and carry out, where breast cancer nurses helped women in one arm to decide between breast conservation or mastectomy using an interactive information programme. "There was little difference between the two groups in their choice, and surgeons around the country said it told us nothing. But we were smarter, and followed up after 3, 6 and 12 months with a quality-of-life and pain exam – and the group with the additional information had less pain and less anxiety. The well-informed patient is half-way on the road to recovery."

Rutgers is clear that a fully functioning breast unit has to be based at a major cancer centre, or be a large facility in its own right. "If a women walks into a breast unit, you don't know if she has cancer and you have to find out if she does, and if so what type it is and if there are difficulties. Without all the right personnel, equipment and treatments you will jeopardise a significant number of women if you are not able to offer everything."

For training surgeons to work in oncology, Rutgers says they must of course specialise in certain tumours, but it is fine to combine two or maybe three cancer types, such as breast and thyroid. "A major part of our training in Amsterdam in surgical oncology is about knowledge of cancer and addressing some of the misconceptions, say, about metastatic disease," he says. "The second component is surgical skills in the chosen tumour types, and from then on it is essential to stay informed about developments, including in the biology of cancer, by attending conferences and technical meetings."

There is little comparative information available about the quality of breast cancer surgery around Europe, he notes. For his part, he has drafted surgical guidelines for EUSOMA, and adds that in the

Netherlands there has been only one audited factor for breast surgery – the rate at which patients have to go back for a second excision after initial breast conserving surgery.

"This has led to one of my biggest controversies personally. Our Inspector General wanted from the National Surgical Society a threshold above which the rate would not be acceptable. We had an existing national guideline of 10% or less re-excision, based on ESSO (European Society of Surgical Oncology) guidelines drawn up by Roger Blamey in the UK. But a list of 100 hospitals published in one of our newspapers showed that 50% of the hospitals were not achieving this.

"I was called by a journalist who asked if it was achievable to get less than 10%, and I said, 'Of course.' Second, he asked if hospitals that do not achieve it are bad hospitals – I said, 'No, but if you have a 30% re-excision rate you need to look at your procedures.' That has put me in a difficult position with colleagues and it is still going on. We all aim for optimum clear margins – two operations is not great but it is not the end of the world." Rutgers recognises that his message about large centres and optimal conditions can seem threatening to those in smaller facilities, but it is one that he is not going to drop.

No doubt it is an issue he has discussed with his closest colleague and friend Laura Van 't Veer, the molecular biologist who led the work on the gene signature (and who was profiled in *Cancer World* May–June 2006). He also counts as a close contact and mentor Harry Bartelink, who headed radiotherapy at the NKI and also the Federation of European Cancer Societies (now revamped as ECCO, the European CanCer Organisation).

Rutgers himself is happy to step up to European duties such as chairing the breast conference – "Someone has to" – and he is confident that his desire for the various societies to be united in 'one strong ECCO' will be realised. "The younger medical oncologists know that the surgeon is my friend and not my enemy," he comments.

Rutgers has two children; one is training in medicine, the other studies industrial design. His wife is curator of a ceramics museum, and they have an extensive property in the north of the country. "I only work Monday to Thursday in Amsterdam. I asked for this some years ago to avoid burn-out, and so I can work on my garden, boat and other hobbies such as playing the guitar and travel. It is one of the best things I've done. You must recognise your limits, and since I moved to four days I've never been more effective. Other surgeons here have done the same."

The aims for the next few years are clear – to get that prognostic and predictive read out and advance optimal breast cancer care, including cosmetic outcomes. And the message for other oncologists is also apparent – if Rutgers is working on a controversial procedure, it is likely to have value, but it will require a lot of thought on how it may work with the patient in front of you.


Best for breast. Rutgers and his colleagues at the NKI were voted the top breast cancer team in the Netherlands by readers of the Dutch women's magazine Libelle, in 2007

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