

Oncology shaping the future of personalised healthcare

How cancer drug development holds the key to success for precision therapeutic approaches

Round table transcript

pharmaphorum media (sponsored by AstraZeneca)

October 2013

Executive summary

Personalised healthcare – ensuring each patient can be treated with the specific medicine(s) most likely to lead to a successful outcome for them – offers the potential to dramatically improve treatment outcomes in a multiple disease areas, with early successes in oncology paving the way for new breakthrough treatments beyond.

A number of challenges threaten the continued pace of development in personalised healthcare. The requirement to carefully coordinate companion diagnostic techniques with drug interventions, raise education about the area and address cost containment issues necessitate much closer collaboration between pharmaceutical companies and other stakeholders.

In this white paper, a transcript of a unique round table debate that brought together representation from the pharmaceutical industry, diagnostic manufacturers, physicians and patients is presented. The discussion offers some insights into new ways of working in partnership that could provide novel solutions for personalised healthcare in oncology, and beyond.

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Forward

Personalised healthcare – ensuring each patient can be treated with the specific medicine(s) most likely to lead to a successful outcome for them – has been a welcome addition to the disease management armoury of physicians since the turn of the century. Without doubt, the development of novel anticancer agents has led the way in this area, with early success stories such as Herceptin (trastuzumab), for the treatment of advanced breast cancer, showing the impact that these highly targeted approaches can have for patients.

However, personalised healthcare has also met with a number of challenges that have limited the pace of its application in oncology and other areas. These include the requirement for accurate companion diagnostics to sit alongside personalised medicines during development and commercialisation, a need for broader education across all healthcare stakeholders and market access restrictions driven by spiralling research costs married with a focus on cost containment from governments globally.

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Ruth March and Paul Tunnah

The solutions cannot come from any single stakeholder, but from getting all key stakeholders to discuss the challenges and initiate long-term broader collaboration to address them. With this in mind, AstraZeneca and pharmaphorum media convened a round table, with the aims of:

- Unify representation from the pharmaceutical industry, diagnostics, physicians and the patient to share experiences.
- Identify potential new ways of collaboration and discuss a vision for the future of successful personalised healthcare.
- Stimulate much broader debate and partnership through filming the discussion and disseminating the outputs through multiple media.
- This white paper represents the transcript from this round table, which sought to address four major questions:
- What has personalised healthcare already achieved in oncology?
- How do we effectively implement personalised healthcare in practice?
- What is the role for pharma in bringing personalised healthcare to the patient?
- What is the future of personalised healthcare?

Filmed in July 2013, the discussion occupied a full day, with the output here representing the published section of a broader debate that continued either side of recording and via individual discussions between the expert participants. To view all media relating to this round table, including the video outputs, please visit:

<http://www.pharmaphorum.com/articles/oncology-shaping-the-future-of-personalised-healthcare-media-hub>

We hope you enjoy the insight offered by this debate and that it triggers further thoughts of your own around how new ways to collaborate can advance personalised healthcare in oncology, and beyond.

Partnership between the pharmaceutical industry and other healthcare stakeholders is important for success here; it is absolutely vital for patients.

Ruth March
VP and Head of Personalised
Healthcare & Biomarkers,
AstraZeneca

Paul Tunnah
CEO, pharmaphorum
media

October 2013

Expert round table panellists

The following expert participants came together to ensure that the debate could cover multiple angles relating to personalised healthcare – the pharmaceutical industry, clinicians, diagnostics manufacturers and, of course, the patient. The discussion was moderated by pharmaphorum's Paul Tunnah.



Ruth March

VP and Head of Personalised Healthcare & Biomarkers
AstraZeneca

Ruth March is VP and Head of Personalised Healthcare & Biomarkers at AstraZeneca. This function includes over 100 experts in diagnostic and biomarker science. The function works with teams in all therapy areas and phases of development to select the right patients for treatment, increase success rates and deliver life-changing medicines to patients.

Ruth has more than ten years' experience in the field of Personalised Healthcare. She has been instrumental in driving over 80% of AstraZeneca's drug projects to adopt Personalised Healthcare approaches. Previous to this Ruth spent ten years in immunology and genetics research at the Universities of London, Oxford and Brunel.

Ruth has published extensively in the field of pharmacogenetics and Personalised Healthcare, has eight granted biomarker patents and is a member of several expert advisory boards.

To read more about Ruth and her thoughts on personalised medicine please visit: www.labtalk.astrazeneca.com/author/ruth-march/

Professor Malcolm Ranson

Professor of Medical Oncology and Pharmacology
University of Manchester and Christie Hospital NHS Foundation Trust



Malcolm Ranson is Professor of Medical Oncology and Pharmacology at the University of Manchester and has been an Honorary Consultant at the Christie Hospital since 1995. He leads a team of clinical researchers at the Christie Hospital conducting Phase I clinical trials focused on apoptosis, cell signalling and biomarker development. His clinical work is closely aligned with the translational biomarker work of Professor Caroline Dive and the Clinical and Experimental Pharmacology group based in the Paterson Institute. He instigated and led development of the Early Phase Trials Unit at the Christie Hospital in Manchester which opened in 2003 and was its Clinical Director for 10 years. The Oak Road Treatment Centre is one of the largest early phase clinical research units in Europe and draws upon a large patient population and is part of the Manchester Cancer Research Centre.

Malcolm is the joint centre lead for the Manchester Experimental Cancer Medicine Centre, funded by Cancer Research UK and the Department of Health to support and develop translational cancer research locally and nationally.

For more information about his work please visit the following pages:
www.manchester.ac.uk/research/malcolm.ranson/

[www.christie.nhs.uk/research-division/research-facilities-and-infrastructure/clinical-trials-unit-\(ctu\).aspx](http://www.christie.nhs.uk/research-division/research-facilities-and-infrastructure/clinical-trials-unit-(ctu).aspx)



Richard Stephens

Chair of the Consumer Liaison Group
National Cancer Research Institute

Richard is a survivor of two cancers and a heart emergency. He has participated in five clinical trials, nearly a dozen other research studies, and currently serves on three trial management or steering groups delivering or monitoring particular research studies. As a patient advocate and representative in health and medical research, his formal roles including chairing NCRI's Consumer Liaison Group, and he sits on several other national and regional committees and bodies, including NIHR, NCIN, RfPB, HTA and MRC CTU.

The Consumer Liaison Group brings together individuals with personal experiences of cancer including patients, carers and relatives as well as representatives of cancer support organisations, researchers and other professionals with an interest in consumer involvement in cancer research as part of their roles. CLG members improve the quality and value of cancer research through consumer involvement and by working with other organisations helps to raise public awareness of clinical research and cancer research in particular. The group acts as a focal point for discussion, advice and feedback to the NCRI, NIHR and wider stakeholders on cancer research issues affecting consumers.

Richard is one of the consumers who designed and introduced the questions on research awareness and participation for the National Cancer Patient Experience Survey, and as CLG Chair he is leading a new partnership with AstraZeneca to set up a Patient Forum, to bring patients and the company's researchers together to discuss trial design and recruitment methods.

For more information about Richard's work with the Consumer Liaison Group please visit: http://ncrndevelop.org.uk/index.php?option=com_content&task=view&id=68&Itemid=115

Mya Thomae

Founder and CEO
Myraqa, Inc.

Myraqa is the leading IVD regulatory consulting firm. Founded in 1998 as a solo practice, Myraqa has grown to include leading experts in Regulatory, Quality, Clinical, Biostatistics, and Development.

Myraqa serves a wide range of clients, including established players up & comers and even stealth start-ups. Myraqa has worked on a full range of IVD applications in the US and EU, including PMAs, pre-Subs, IDEs, 510(k)s, de novo 510(k)s, and EU technical files.

Mya Thomae has almost 20 years of experience with regulatory and quality, much of it as a consultant and later as founder of Myraqa, Inc. Prior to becoming a consultant, Mya learned the ropes at Chiron and OraSure. Mya has been involved in numerous successful applications before FDA for clients in the US, Canada and EU. She worked with FDA to develop the special controls document and regulation for microarray devices and helped establish the precedent for parallel 510(k) submissions. Mya received a Commissioner's Special Citation at the 2009 FDA Honor Awards in recognition of her work to clear the ABI 7500 Fast Dx.

For more information about Myraqa please visit the following page:
www.myraqa.com



Paul Tunnah

CEO and Founder
pharmaphorum media

Paul is the CEO and Founder of pharmaphorum media, which provides content and social media marketing and communications solutions for the pharmaceutical sector and also manages the industry leading channel, www.pharmaphorum.com, a digital podium for communicating thought leadership and innovation within pharma.

Prior to founding pharmaphorum media, Paul has a strong background in commercial pharmaceutical consulting, digital media and content marketing. He has written and produced numerous articles and reports / white papers during his career, recently co-authored the 'Digital Unlocked' guide to digital pharma, is regarded as a key industry advisor on social media communication and has developed pharmaphorum media into a globally recognised industry brand, engaging with senior industry executives on key issues and connecting them with external thought leaders. He received both an MA in Biochemistry and DPhil in Biological Sciences from Oxford University.

For more information about Paul Tunnah please visit pharmaphorum:
www.pharmaphorum.com

Introduction and part one: What has personalised healthcare already achieved in oncology?

PT: I'd like to welcome our expert panel here today to discuss 'oncology shaping the future of personalised healthcare', and specifically how cancer drug development holds the key to success for precision therapeutic approaches.

Just to introduce everyone to begin with, we have Richard Stephens, Chair of the Consumer Liaison Group at the National Cancer Research Institute in the UK, and in that capacity you bring the important voice of cancer patients, caregivers and relatives into research, and I know you're facilitating some really interesting work with the industry as well, so welcome.

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Paul Tunnah

On my left we have Ruth March, who is AstraZeneca's Head of Personalised Healthcare and Biomarkers, and comes with around 20 years' experience in the genetics and personalised healthcare space - welcome Ruth.

We also have, over from the US, Mya Thomae, who has a particular interest in the diagnostics side, and is Chief Exec of Myraqa, with over 20 years' experience in the in-vitro diagnostics space, and a particular interest in personalised healthcare as well - thank you for joining us today.

And finally we have Professor Malcolm Ranson from Manchester University, where he's Professor of Medical Oncology and Pharmacology, and also Honorary Consultant at the Christie Hospital. Malcolm has a particular focus on apoptosis, cell signalling, and biomarkers, so brings an important research aspect to this discussion.

We're going to be talking about a number of aspects of personalised healthcare today and, just to set the scene, obviously it's been a very hot topic for a number of years now, perhaps heralded by some of the early successes with drugs like Herceptin, first launched in 1998. If we look at where we are now, that significant promise, to some extent, may not have been lived up to, but equally some people say we're now at a stage where personalised healthcare is really about to take off. There are signs of a number of new drugs coming through, with almost a third of the drug approvals in 2013 being linked to a companion diagnostic approach, already so far, and around 600 industry-sponsored trials taking place with a companion diagnostic element.

Equally we know there are a number of challenges with the regulatory landscape, with the reimbursement landscape, and indeed in education around the personalised healthcare space. So we'd like to cover off a those angles today. We'll go through a number of different topics relating to this.

I'd like to start with your views on what personalised healthcare really is, and what has it achieved so far in the oncology space. I'd like to then move on to look at the healthcare systems, what is it that is perhaps missing or needs to be advanced in order to get these medicines to patients, and we will then critically look at the role for the pharma industry in this debate, how pharma needs to develop and partner to bring these medicines to fruition.

My sense of personalised medicine is finally combining the expertise that exists in pharma, and in diagnostics, and trying to bring those together

Mya Thomaee

And finally if we look at what we've learned in the oncology space I'd like to look beyond and say where is that taking us, what is the future of personalised healthcare beyond oncology, and what can we take from this. So I think a good starting point for this is to look at how we describe personalised healthcare. There's a lot of terminology around this - we have personalised healthcare, we have personalised medicine, stratified medicine, people now talk about precision medicine. So I'd like to understand your definition of what is personalised healthcare, and perhaps Mya - you'd like to kick things off with how you view this space, how you would describe it?

MT: Well, being a diagnostic person that's really my focus, and so there's an incredible amount of work that goes into developing these compounds. Finding the right test with the right cut-off, with the right sensitivity and specificity is really key to a lot of this. So my sense of personalised medicine is finally combining the expertise that exists in pharma, and in diagnostics, and trying to bring those together. It's tricky, there are a lot of issues that make those industries very different, and how research is done in those industries is very different. So I think we've made a lot of progress in it, but there's still a long way to go.

PT: Malcolm, looking at that from the research perspective would you say that's pivotal and that is how you describe personalised healthcare - that mix of drug and diagnostic?

MR: Well, I guess as a clinician you see it in perhaps slightly different terms, and personalised medicine to me, having grown up with it over the last couple of decades, is really that ability to use molecular diagnostics to tell us which patient to treat, to try and be a little bit more, as you phrased earlier, about precision medicine. People talk about the right drug, in the right patient, at the right dose. We even now talk about it (since we're thinking about cancer patients moving through their cancer history from early diagnosis through to refractory disease) as also needing to be at the right time, so in the right frame from that perspective.

PT: From a cancer patient's perspective what does personalised healthcare mean to them?

RS: To me it's not personalised if it's based on something like DNA molecules or genetics, because I'm a person. I know those things are part of my make-up and biology, but actually I think and I feel, and there's something more sentient to personalised medicine. Personalised healthcare then goes down the route not just about what treatment you're having and what the diagnosis is, but it's actually about where you're treated, and are you actually at a hospital, depending on what your condition is, that will treat you as an inpatient, or do they prefer to treat you as an outpatient.

I think stratified medicine, as we tend to call it as patients working in cancer research (the idea that we're working on things that fit particular molecules in particular groups of people with particular conditions), that's quite different, and I think breast cancer over the past 10 / 20 years is a very good example of where we have made advances. Some of the blood cancers, for example, are now virtually chronic conditions. But there are other cancers, pancreatic cancer, where there is virtually no progress.

So again, I think we're at the stage where personalised healthcare, or even stratified medicine, is not about cancer. It's about cancers and which one you've got, and there are many patients who will still actually divide it

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Richard Stephens

into two types - there's the type of cancer that you're going to get over and there's the type of cancer that you aren't. I personally think we are a long way from truly personalised healthcare, but the advances we've made are in molecular medicine and targeted therapies, and that's different.

RM: Yes, it's very interesting hearing the views of everybody and the different opinions. I must say that a few years ago we became aware that there were many definitions of personalised healthcare, or stratified medicine, or targeted therapy, or whatever you want to call it, and we came to the conclusion it wasn't that useful to talk about the best phrase or the best definition.

What we're talking about, as a pharma industry, is realising that when we produce drugs it is about more than just those molecules to treat patients, it's about the whole experience, about knowing what the diagnosis is, about the test that you may use, whatever goes around that so that the best treatment gets to the right patients. So it may be a molecular diagnostic that we use, or it may be something very simple like family history, or a clinical algorithm that just looks at the patient characteristics. All of those to me are personalised healthcare and we are using all of them to get the right drug to the right patient.

MR: One of the sea-changes, the transformational changes, that I see occurring between what used to be empirical cytotoxic chemotherapy and more targeted therapy is that the quality of life difference that the patient experiences when you get personalised or stratified medicine and healthcare to work is really a very different feel. Coming back to the earlier point of whether it's useful to bring that out more into the open – yes, I think patients could really describe that sense of difference, because many of them have experienced both empirical cytotoxic treatment and the more targeted personalised medicine approaches, and they will describe it as being transformational.

RS: There is too the other side of the coin to that. I was really interested that the US are using a term precision medicine, which I have to admit I had never heard before, but it strikes me as quite important, because the other side of this agenda is knowing which things will not work in certain patient groups so that you don't give people drugs that are going to do no good whatsoever. This is particularly important if you do have something else that might be available - a stem cell transplant, for example, or something like that. And I think that's the other side that we sometimes forget, finding out why things don't work in some groups of patients is equally important.

MR: So it is about both sides of the coin...and avoiding toxicities, because equally, personalised healthcare approaches can be as much about dealing and avoiding toxicities as it is about efficacy.

MT: I think precision medicine has taken over in terms of an academic discussion about it, and maybe even an industry discussion about it. But if I said that to my mum or my brother I don't know that they would know what I am talking about. I could talk about that, but they wouldn't get it. So I think from the folks that are working in the industry I think that term is [known], but even at FDA they have an office of personalised medicine now, so they have taken on the personalised medicine moniker.

PT: If we just step back from some of the language that's used around personalised healthcare and if we look at the oncology space - has personalised healthcare delivered and, if so, what do we regard as really good examples of delivering success?

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Ruth March

RM: To me again it's the transformational effect of some of those early examples. I would think of drugs like Herceptin, which was originally approved for 20% of the breast cancer population [and] within five years was treating (for the patients that had the appropriate biomarker) over 90% of that population. So for those patients that had a worse prognosis and had very little treatment available to them Herceptin then became almost the standard of care.

Similarly Glivec [(Gleevec in US)], which had a very difficult time getting backing within the industry because it was directed at such a tiny population, became a clinical and a commercial success, not because the population was large, but because those patients who took it stayed on it. So rather than actually dying within a few months they went on to take Glivec for a much longer period of time, and suddenly this became a drug which pharma was interested in. In fact I think there have been six follow up drugs at the same population and for those patients that develop resistance. So these are the sort of examples I think of which transform the industry.

PT: The key question you must be asking, as anybody in the industry is asking, is what did we get so right with Herceptin and Glivec that we need to do moving forwards? What's your view on that?

RM: Yes, well I think the key thing many of us in the industry have realised is that you need to start early. If you select patients in phase I, in a clinical trial, and then you see the response (there's been recent examples of that, like crizotinib) then you see a remarkable result. Then you know that drug really is going for the disease mechanism of the biomarker in the population that you're picking out. So I think you then have a compelling case to take to the regulatory authorities, and of course you may get early registration, and you may also get the reimbursement that's so important, particularly in the US.

PT: Richard I'd like to bring you back in here, because as well as dealing with a number of cancer patients you have been a cancer patient yourself. You've got a very personal aspect on this, so for you has personalised healthcare delivered in the oncology space?

RS: Well I'm still here, so yes! But that is a very personal view. I think if you simply look at the numbers then, yes, because we have many more people surviving cancer for much longer than there used to be, and some of that is down to personalised medicine. For me actually, yes, it's really good news, and for lots of other people it's really good news. But we still don't have enough of these treatments in enough cancers, and I do have some concerns that what we're doing, because we're so interested in molecules, is we're going down narrower and narrower fields. When I sit on things like funding committees now, more and more trials coming forward are for smaller trials in much smaller groups of patients, which is really good news for them, really good news, and we want to go down that route. But at the same time I'm genuinely not sure that we're ever going to have big impact drugs again.

PT: So it's not a straight yes or no - we need it to work for more people?

MT: And I think you might be very interested at a [recent] FDA meeting. This is actually a lot of the concerns that they express when we do want to select very early on. They are concerned that maybe there is activity for a larger group of people than we're willing to study with that drug. So it is difficult. I think Ruth's point is really important - you can target the folks that are

really going to respond to the drug, but they're very concerned that we are narrowing it too much [and] maybe there is benefit for a lot more people than that selected group.

MR: As Richard has alluded to one of the real dangers of personalised medicine is that we create areas of medicine, areas of unmet need, that simply don't get addressed because there isn't a commercial avenue that's open, or it's a harder area to crack. In the end we create more and more Cinderella disease, albeit in perhaps smaller populations than existed in our old empirical model.

Part two:

How do we effectively implement personalised healthcare in practice?

One of the challenges that we really have to address is that an explosion of molecular medicine has certainly left quite a lot of physicians behind

Malcolm Ranson

PT: In terms of the understanding of application of personalised healthcare by physicians and those in the broader healthcare system, what do you see are some of the challenges there?

MR: I guess one of the challenges that we really have to address is that an explosion of molecular medicine has certainly left quite a lot of physicians behind, and therefore their ability to track and to follow some of the developments because of the pace of them is a real challenge. All of a sudden, instead of seeing a group of breast cancer patients and having a very simple algorithm to work with in terms of a treatment decision, it becomes much more complex and there's much more information to assimilate and bring to the table.

PT: The industry has always been involved in supporting physicians [via] medical education, so what level of understanding in personalised healthcare do you see in your interaction?

RM: So again I think it's enormously varied. When we work with academic or medical centres they're usually ahead of what we know. The centres that we work with are key opinion leaders, are doing medical research in their own centres - they're using cutting edge technology, they're running clinics, maybe running their own trials where patients may be treated according to their biomarker profile. Then when we're going out and running clinical trials globally, we're into a completely different paradigm - we are working with many centres (it can be thousands of centres all over the globe), we're working with different ethics committees, and translating documents, and that level of education may be very challenging.

PT: So there's almost some regulatory hurdles here and perhaps lack of consistency on a global basis with the regulatory environment?

RM: Yes, because of course the regulators and the ethics committees want to make sure they are protecting the patients, and that is very understandable and that's their job. It may come to a stage where, because the pace of the technology development is going so fast, that this actually becomes unrealistic. I remember a situation not long ago in Japan where we had to specify not only every gene [that] should be tested but [also] every variant of the gene to be tested and every technology and test to be used.

MT: Well there are also technical issues too. When you have a tumour sample there's only so much of it. So that's been a lot of the discussion [about how] we can look for all these different biomarkers now, but we may not have sample enough to do everything that we want to do.

PT: I wonder about your view on this Richard. Are those blocks on the regulatory side, or is that more in terms of the practical aspects of healthcare systems?

RS: All of those and probably more as well. In this country the clinical trials I see day after day run past me just for a comment on patient information, have a cut-off [age] limit of 60. I understand that there are perfectly good reasons, in terms of the power of these drugs and things, for wanting that

Sometimes I almost feel like the diagnostic information is overwhelming... we just need to stop on some level

Mya Thomee

cut off limit at 60, but if the majority of cancers occur in elderly people, and we're talking about personalised medicine, how can we leave out the biggest chunk of population?

MR: We have to start off with patient populations where safety, tolerability, adequate organ function is part and parcel. Regulators, ethics committees, patients, all expect that. We also have to remember that a lot of tumours are not necessarily going to be amenable to the single hit, or the single biomarker paradigm, that I've just discussed. Potentially we may be looking at an elderly patient, perhaps with a lung carcinoma that's got a very complex abnormality, multiple genes, lots of different genes, and therefore we don't really know what is drug-able what isn't; what combinations we might need to use, or even whether anything will work. To some extent what we face at the moment, between the diagnostics market with the multiplex platforms and our ability to garner information that tells us a lot more about the biology of the patient, is then actually being able to know what to do with it. And I think that is going to be a real issue going forwards in trying to handle information where we yet don't have the answers.

MT: Well I think sometimes the information bank is almost too full. Coming back to Ruth's comment about trying to conduct clinical trials across the world - trying to find a single test that you can use across the world, and in real people on any kind of timely basis in these trials is a pretty high goal to reach. We often end up having to use multiple different tests to get enrolment, and then use another test to see who really is positive based on a specific test. Sometimes I almost feel like the diagnostic information is overwhelming...we just need to stop on some level. But each hospital, each clinic, has their own test. They want to use that test at the end of the day, we have to have a single test. It's a very tricky amount of information to handle.

PT: How robust are those tests between themselves - are they consistent in their results?

MT: Really good question [laughter]. Even in the United States we have this bizarre two tiered structure for regulating the diagnostics - some laboratory developed tests, some FDA approved tests - and it's very difficult to know whether those tests match up, whether they're getting the same mutations, whether the sensitivity of those tests is similar. It's very difficult right now.

PT: How big a problem is it Ruth, at the moment, from a regulatory standpoint where you've got these trials with potentially different tests being used in different regions. Is that a big hurdle for the industry?

RM: The thing that we find most challenging is the difference between different regions. So Europe has what I would call a very pragmatic approach to diagnostic testing, which is that it's separate from the drug approval. So a therapy will get approved on the basis of how safe and efficacious it is in the indicated patient population, and if a biomarker is used to define that population then there is a separate process to regulate the diagnostic test. In the US that has its own challenges, mostly in terms of timelines of clinical trials and drug approval.

It's all done for the best of intent, and in some cases it can work really well, where the marker for the diagnostic is so obvious that it's known right from the first phase of the drug development. But that's actually pretty rare. So if there's any research that you need to do during drug development

it becomes very challenging to get the diagnostic development and regulation in on time.

RS: But from the patient perspective, when we're being sent for tests or told to have tests, we tend to accept what the doctor in front of us is saying about the test. And then we go away and we read something else, or someone else says something else, so it's almost right at the start of the treatment. If we're doing personalised medicine how can we have faith in the personalised medicine if we start to doubt the test itself that's producing this result? Personally, as a cancer patient trying to work in cancer research, more research into accuracy of diagnostics is one really key area.

MR: And it gets more complex still. I talked earlier about this business of patients being on a cancer journey. I see patients at the phase I level when they've already had multiple treatments. Clearly the tumour tissue, the tumour that I'm dealing with, as I say to patients, is a completely different beast from what you started with - it's a subdivision of what you had to start with and it's now gone through metastasis, it's now become multi drug resistant - and what I am looking back at is your original biopsy because that's the material I've got in the laboratory I can look at. So we have to say to patients much more regularly now, 'look I know it seems to you that this is a bit of a step to take, but we actually need some more tissue out of you', or, 'we need to go after that particular piece of tumour', so that we can actually identify what your tumour looks like now, we can't rely upon historical data. And that again is sometimes an ethical and a practical challenge.

RS: As you have said, but didn't use the word, cancers evolve, they don't just spread around the body, which we can understand. The idea [is] that you start off with a cancer which behaves biologically in a certain way, and if you've still got it a few years later after all the drugs we say things like 'it comes back'. Well, the chances are, it didn't go away – there are just two or three cells and they have changed. And what you're actually fighting, we might still call it a metastatic disease from the first cancer, but actually biologically it's different, it's completely different, and it may well be of course completely and utterly personal to you, which is where the personalised medicine will then fall down, because you are the first person.

MR: We need to think about the disease in a much more longitudinal way, and we need to think about tests in a much more longitudinal way, and think about the practicalities of how we do biomarkers in that longitudinal journey - the cancer journey - that patients have.

RM: So that brings up a very interesting point. We were talking about 'are we simply going to smaller and smaller populations' and what about the patients, if you like, who get left behind, and then there isn't a treatment for their particular cancer. So we are just now starting to see the new generation of drugs which have been designed from the understanding of these resistance mechanisms. And from the biomarker research, from the original medicines, then you can see how the biomarkers change as tumours do become resistant, and then you can start to design drugs from the start to address those resistance mechanisms. And these drugs are very early in the clinic but they are starting to come through now.

Cancers evolve, they don't just spread around the body, which we can understand

Richard Stephens

Part three:

What is the role for pharma in bringing personalised healthcare to the patient?

PT: If we look at the role for the pharma industry [in personalised healthcare], is this fundamentally going to change the drug development process?

RM: I believe it will - I believe it already has. We are looking, at AstraZeneca, at 80% of our drugs in the pipeline following a personalised healthcare approach. That's not just oncology, that's all of our drugs, and I think that's a high proportion for pharma, but it's not unusual. There will be other [pharma companies] that have the same, and that then changes the whole way we do drug development, having that patient selection paradigm in our clinical trials, allowing for the biomarker testing, all the infrastructure that we've been talking about, and the transmitting of biomarker data - that's a big change to how we do business. I think it will make us much more patient-centric.

PT: So this is a great model for patients - more tightly defined patient populations, better testing, in theory better drugs that are more efficacious. It's a challenge commercially because the drug development costs don't necessarily decrease proportionate to the patient populations, and we're talking here about the whole issue of who pays for all this. How do we tackle some of those issues?

RM: We're living in a world where there are generic drugs available that are effective and that are much cheaper than the novel drugs that are coming out of the pharma industry. So the challenge for the pharma industry is - what is it that we do better? For those generic drugs what is the value proposition for the people with the health budgets? And it has to be those populations where we can show clearly that the efficacy, the safety and the benefit to patients is much better than we would get in the broad population. Those can well be those populations that we access using personalised healthcare and diagnostic tests.

RS: If you have a company like AstraZeneca who is willing to take us on, and there are other pharmas doing it as well, I think that has to be the way forward. The idea that instead of looking at it like 'we have an interesting molecule, what can we do with it?', you actually have a situation [more like], 'in patients this is how the cancers are changing - how can we stop it, as opposed to attack it'. That's a far more patient-centred approach and, I'm afraid politicians won't like it, but from the patient perspective the money being spent is well spent if it helps more people survive cancer a little bit longer, or preferably a heck of a lot longer.

All that presupposes that the drug development works, and our interest is that all the information about drugs that do trial is made available to other researchers, because that's why patients do go into clinical trials. Of course [in] phase I trials there's always the hope of the miracle cure, but actually what links us all - phase I, phase II, phase III - there is the knowledge that we are going to do some good for somebody else, and that does mean that whatever comes from that trial should be made available and should be shared.

RM: That's absolutely something we subscribe to. We have committed to transparency on all our clinical trials and those trials are made available

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Ruth March

We see this space of personalised healthcare and diagnostics as a really fertile area for partnerships

Malcolm Ranson

on our website. But I think what Richard is really talking about here is beyond that the concept of taking drugs which maybe haven't been successful in our large clinical trials, and making those available. So we have announced, and have in process, an open innovation with the Medical Research Council in the UK, the MRC, where we make [molecules] available to researchers, so that they can try out these molecules that have been tested in the clinic on any patients that the physicians think are appropriate. If those are successful we still have the option to take them back in, so it's really a win-win situation. We also have that situation with the NIH in the US and it's an area where not only AstraZeneca, but other pharma companies, will be doing more and more of this type of open innovation in the future.

PT: It has to come back to having the right diagnostics doesn't it?

MT: It does. But also giving the investigators some freedom to do these things that maybe there isn't a massive amount of data on. That's one of the things that we've been working with FDA a lot on, is for these investigator sponsored INDs where they do want to go off, they have a hypothesis but maybe not a lot of data, is convincing the IRBs, convincing FDA that's an acceptable way to go.

PT: And we have two quite different industries trying to converge here. What is the right timing for that interaction and how do these industries work together to develop this process?

MT: We're still working on it. I think some of the [pharma companies] have adopted the process of buying their own diagnostic companies so that they potentially have a little bit more leverage. Now that seems to get out of sync too, so you don't always see drug companies that have diagnostic companies necessarily working with their own diagnostic companies, so you get into some interesting situations there. But really I think it's being willing to work together early on before anybody knows if there's commercial interest too.

So we're still working on it, but I think everybody sees that this is going to be good for all of us in the end, and we're trying to work on that. And I think we're going to eventually blend [into one] industry - there will stop being this sharp demarcation between pharma and diagnostics, we're going to become a biotech industry, because I think it's no longer a division - we're going to blend eventually.

PT: How does that present itself in the clinic Malcolm? Do you see this as two very separate industries, or do you see more collaboration between them?

MR: We see this space of personalised healthcare and diagnostics as a really fertile area for partnerships, both between commercial and commercial companies, or commercial and academic, commercial and university. It really is very fluid, it's very dynamic [and] it can be extremely synergistic. Providing we think about bringing the biomarkers early enough to the process of development, providing that we have a relatively open pragmatic approach to sharing data, and that we then design clinical trials (if they're adaptable) that can be iterative in terms of improving and following leads, or closing down areas where we feel that investment is no longer required, then I think we can bring success to what in a sense is a very diverse and somewhat complicated development process.

PT: And from your perspective would it be easier if perhaps diagnostics capabilities were held within pharma companies?

I think the payers are trying to do the best thing for patients, and to make sure they are getting the right therapies

Mya Thomae

MR: No, I think there's space for a plurality of provision. I think particularly in the pre-commercial space then there's plenty of opportunity for commercial-academic collaboration. Clearly at the late end, when it needs to go out to the FDA and regulatory authorities, then that merger of biomarker test with therapeutic needs to be brought together, and I think the pharma and biotech industry will have an inter-digititation that moves and flexes apart over time, but will ultimately come closer together.

RM: So we have looked at this many times, and our conclusion has always been that we get the best flexibility through partnering with diagnostics companies. But we do try to set up strategic alliances with those diagnostics companies as far as possible so that we're not bringing the company in at the last possible moment. That does sometimes happen, but it's much better, as Mya said earlier, if we can sit together right at the start of the project and look at the respective pipelines and see how those could work together. We do pay for a lot of the development costs of the diagnostics company. When a drug fails in late phase and a diagnostics company is involved, if they have invested in that diagnostic and then they lose it through no fault of their own that can be devastating for a small diagnostics company. So we do reckon to subsidise that.

MT: I think there's been a lot of interest in creative, I don't know if you call it financing or creative partnering, in order to make that work out for everybody. [With regards to] some of these biomarkers and some of the things we've been talking about with tumours changing, there will be tests that need to be done more frequently. This was a huge change, for example, for HIV. When HIV monitoring came in, that was really a perfect storm of not only an endpoint being available with that diagnostic, but really propelling the drugs and what was being developed there.

And I think we are starting to see that with the test as the mutations are changing, where the testing needs to be performed more than just once to really find out what's going on with that patient. So as that part of this progresses, and I think we're still a little bit away from it, the diagnostic industry will be more interested and see the maybe a similar arc in revenue as the pharma companies have.

PT: When it comes to healthcare systems and the payers within them, one of the challenges of personalised healthcare is you're now asking them to pay for potentially a drug and a diagnostic. What's your sense on [if we have] got enough development there - do payers understand the value of these diagnostic systems?

MT: One of the challenges that we have in the United States is the payers can't necessarily see what they're exactly paying for. Are they actually paying for the FDA approved tests? Are they paying for some kind of laboratory develop test? Is there anything the payers can do to insist upon the FDA test? So that's been one of the big discussions that has been going on as well. I think the payers are trying to do the best thing for patients, and to make sure they are getting the right therapies, it's also in their interest not to have patients trying 10 different therapies, [because] that's obviously a difficult situation from a cost perspective as well. I think it's coming together, but we've got a long way to go.

RS: The issue about diagnostic and paying for diagnostics is interesting, because again if you look at the way we try to manage things in our country at the moment, with a National Health Service, ultimately the bill for people who are sick gets paid for by the NHS. It's not a health service - it's a service for people who are ill; Public Health England is

We have some situations where the payers are actually driving the discussion

Ruth March

now separating out the prevention side. But to me that's where we might be looking at some real cost savings in diagnostics, and it's in terms of diagnostics where it produces risk management and sensibly designs screening programmes, so you can actually start to filter some people out, and you can start to deliver some interventions earlier which may be quite cheap interventions.

If you look at diagnosis on the assumption it's going to find something which then needs an intervention that's one cost model. But actually, if you look at diagnosis in terms of prevention, risk management, [then] there are then savings to it. I don't think we have the model yet that will actually tease those out. So it's another one where I think we're on the cusp something that will change significantly.

RM: We have some situations where the payers are actually driving the discussion, so there was historically a case in the US where some personalised medicine advances were made in two drugs (I think for colorectal cancer) and it was actually the payers that applied [pressure] first before the FDA actually approved them, because they refused to pay for those drugs unless the patient had the appropriate biomarker. Then of course you have the other side of it, which we've been referring to, which is about payers wondering where this testing budget is going to come from, because the reimbursement systems for testing are different every country you go into. That's quite simple in some countries and very complex in other countries.

MR: But just as in the past where we've come up against discussions about where funding in the UK should be applied to, small increments in progression-free survival or survival, we will come up against the same discussions with healthcare payers and so on in and around the grey areas with biomarkers. We probably then have both to contend with down the line, so we're not going to get away without those discussions being had.

Part four: What is the future of personalised healthcare?

PT: If we look forward in terms of 'what is the future of personalised healthcare' there's obviously some key lessons from what has taken place in the oncology space. Looking at it from an industry perspective, Ruth, you're looking at not just oncology within personalised healthcare. What are the key things that you take from your experience in oncology and [that apply] to other therapeutic areas?

RM: Well I think it's very much some of the same lessons that we've seen - the ability to select the right patients for the right drugs, and starting early and working with our diagnostic partners. One of the most exciting areas for me is in neuroscience and diseases like Alzheimer's disease, where again there may be a long period before you actually know that a patient has Alzheimer's, and even getting that differential diagnosis very early may give you more of a chance of intervening and developing drugs. So as we work together to develop drugs in our pipeline I think that's a great area where we will be able to apply some of the same lessons that we have from oncology and take these drugs through, and develop drugs that will be life changing for patients.

PT: What about from the patient angle Richard. You've done quite a lot of work in terms of bringing the patient voice into the drug development process. What have we learned from oncology?

RS: There's two separate strands to that. I think one is the patient voice in terms of how we work with AstraZeneca, and other companies, in talking about the research agenda. But actually that conversation is part of a much bigger one, which isn't really a conversation [at all], it's just simply what's already happening. More and more of the research trials, the interventional trials coming through in cancer in patients in the NHS, are around the stratified medicine agenda, and what we've seen is that patients don't necessarily need to understand the scientific concepts or the detail of the molecular biology.

What's happening is that they are joining those trials in greater numbers than before, and they're not just consenting to the main part of the trial, the test of the intervention, they are [also] donating tissue, they are donating samples, and again in much greater numbers than ever before. So I think part of the patient conversation is that we're not just talking about it, we're doing it. We are contributing, because we believe that this is the right way forward, and even if we're not going to be helped by a particular piece of research, we do understand that research is designed to help people like us - same symptoms, same disease, same biological markers or whatever it may be, in the future.

PT: So there's a real willingness from patients to get involved even if there's no personal benefit potentially to them?

RS: Whatever the reputation problems there may be about big pharma these people are making products which help people like us. So actually we are going to sit down, we are going to talk with them about how we can improve that process so that those products help more people more quickly.

MR: What I see, since oncology has been at the leading edge of personalised healthcare in many respects, is that what can be applied elsewhere is

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Ruth March

really this business of accepting that each individual organisation, be it pharma or biomarker or academia or healthcare providers, we don't have all the necessary instruments or expertise to pull off personalised healthcare [alone]. We really need to have a more sharing relationship, sometimes longer term relationship, to make that development possible. That therefore means that each organisation has to be outward looking, but also it needs to really have first class interface management, and these partnerships, these arrangements, the synergy if you like that we're trying to build, can fall down unless we have people with vision and people with good interface management.

PT: Who is the key driver for that; who is going to be the co-ordinator and really help bring those different groups together?

MR: Well since a lot of the developments in therapeutics are coming via industry and from academia, I don't think that we can necessarily assume that there's a dominant partner in this. We have to accept that it's a much more inter-digitated relationship than perhaps we've been used to. So I think we've got to, I was going to use the phrase 'get in bed together', make it a whole. And I think that does need people with vision on all sides.

The patient will not accept, nor should anyone else, a test that [takes] two months to come back

Malcolm Ranson

PT: What have you learned in oncology from the diagnostics side and how does that model need to develop beyond oncology to work?

MT: A lot of what the diagnostic industry is focused on is technology, and we have done a great job of it. We have next-generation sequencers, we have multitudes of different kinds of sequencing, PCR things like that... and the diagnostic industry, with these partnerships, is going to become more aware of the uses of those technologies. Rather than focusing on just developing a faster sequencer, [it will be more about] what do we need in terms of those sequencing technologies paired up with the information on the biological relevance of these markers and how can we exploit the technologies that we have today.

But again, not leaving out the patients, in HIV the reason a lot of what happened was because there was a united patient population that demanded different kinds of clinical trials, demanded that drugs not necessarily have to go under quite as much scrutiny before they be given to patients. That community really wanted to accept the risk of taking drugs that did not have as much development behind them and I think that we are going to see that in oncology, we are going to put pressure on ethics communities, on IRBs. As the cancer communities come together, as people live longer with their disease, there is going to be more pressure from that part of it for us to do a faster, sort of different job, in what we're doing with both diagnostics and companion diagnostics.

RS: I think that's a really important point about the risks, and one of the huge advantages we have now in this country is what the National Cancer Intelligence Network has done with hospital episode statistics and all the data available from cancer registries, so patient groups can become far more aware about their long-term risks, long-term prognosis after certain types of treatment. Once patients get hold of that, and the researchers get hold of it, and start some stats and information from that there is a whole world of opportunity opening up and, oddly enough, it's driving personalised medicine from the use of masses of pieces of information about thousands upon thousands of people over very many years.

PT: If we look forwards, what do we think are the most exciting technology developments that will really push personalised healthcare forwards?

MR: In terms of trying to deliver technologies in a clinical situation we need the testing to be delivered within a meaningful timeframe. The patient will not accept, nor should anyone else, a test that [takes] two months to come back and then comes back saying 'I'm sorry but the sample you sent us was not of sufficient quality or didn't contain tumour cells'. We really have to have infrastructure and mechanisms that allow both high quality samples and rapid turnaround.

[That's] one of the things that came out with Swanton's definition of the evolutionary tree of what a cancer might be. Yes, that's all very fine, but that data took four months to produce in one handful of patients [and is] clearly not going to be applicable unless we completely turn things around in a much larger patient population [that] it's got to be [in to be] useful clinically.

RM: The next generation sequencing is something that's been on the horizon for quite a long time - it is used in very specialist centres, probably being more useful in some situations than others, but the speed is increasing all the time. The cost is going down, which of course is what we need, and what's really critical, going back to the same point, is the ability to analyse that data and pick out what is going to be useful for the various patients, which differs in the disease setting.

Another area that I think is vital, and again going beyond oncology, is the ability for rapid diagnostic testing, and we particularly see that in infection. So if a patient comes in with a serious infection, something like MRSA, you don't have time to send off a test for two or three months, or even two or three weeks - you really need an answer right then and there by the patient's bedside so that patient can have effective treatment. We are starting to see these technologies that can do that, but they are in the very early stages, and then back to the promise of imaging, so we are always limited, we think, in terms of tumours and other samples - is there a part of the patient that I can take out, look down a microscope [at] and take away to the lab. If you're in neuroscience, or if you're dealing with other areas, maybe brain cancer, you can't do that. So having the ability to use molecular imaging that sees the progress of the disease as it is going on within the body, I think will be transforming in oncology and also in other diseases.

PT: So are we at the start of a much deeper up curve in terms of technological advancement here?

MT: To some degree we're trying to catch up on the assay side to the technology that has already been presented to us. So again there is, when you're developing a diagnostic that you need to have it be a stable test, diminishing returns to having it be 30 minutes faster, or things like that. We have several clients that are working on this closer to patient care rapid technology, which doesn't have the breadth that something like next-generation sequencing would have, but once we know several of the genes, and maybe some of the genes and mutations that are in common with some of these drugs, some of these faster technologies, I think could create almost as much disruption and change as something like the next best sequencer.

RS: The technology is fabulous, but I think much more importantly there is all this willingness to actually use it and get on with the job.

PT: So there's willingness there, we know we want to get to this solution, I guess the question is what does this look like? Where do we need to get to,

We have several clients that are working on this closer to patient care rapid technology

Mya Thomaë

What it looks like is full multidisciplinary working with much more open sharing of data

Malcolm Ranson

what does that success look like for personalised healthcare?

MR: What it looks like is full multidisciplinary working with much more open sharing of data. Doing that a little bit earlier on, spending more time in the translational research space and the early phase space, where a lot can be learned about a therapeutic and about the choices that we need to make for late stage studies. To make sure that we have research that is flexible and adaptable, we make sure that we get other partners, the ethics committees and the regulatory authorities thinking along those lines. That we don't have all the answers - the technology is moving very quickly, [so] we need to be able to adapt and progress in an efficient and non-bureaucratic fashion.

MT: I think success, coming from the diagnostic industry, is to not have to say 'I'm from the diagnostic industry' anymore, to say that we're in this together, that we're in the personalised medicine business, and we're no longer making those distinctions. So there is always going to be expertise, there is going to be some distinction, specialisation, things like that, but I think success really will be when we stop seeing this even as partnership - we're all working on this together. Everybody wants to figure out a way to do this, and once we blend a little bit more and figure out how to do it together we will make even more progress than we've already made.

RS: I like the idea about more informed discussions between both those giving the treatment and the patients, and one sign of the success [is that] patients are quite happy to deal with pharma; it's the general public who have a perception. So I think if we can change the public perception about pharma and indeed, perhaps sometimes too about technology, that would be a step forward.

But in terms of patient I have two simple things that I would love to see, which is that every single patient, regardless of their age, has some sort of opportunity to take part in research, not necessarily an interventional study, but actually some sort of opportunity to take part in research, that will be the first thing. And the second thing is that every single patient asks about the opportunity to take part in research, whether or not they actually choose to do it, because that will always be the patient's decision.

RM So success would look like [that for] every drug in our pipeline we would be able to know what was the best patient population for that drug, and that we would be able to design that drug so that the mechanism of the action, of the drug, the biomarker and the patient would all line up very early on, so that we would be able to have much more successful drug development, [so] that when those drugs came onto the market then they would be transformative, they would be life changing for the patients that took them. I'm privileged to have taken part in the drug development of some of those drugs already in my career, and before I retire I want to take part in the development of a lot more.

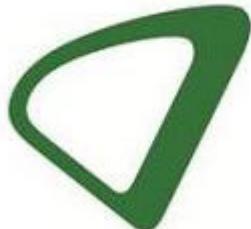
PT: There's been a number of themes permeating the discussion today, and I think for me they come down to three core areas. One is around a new innovation process - we've talked about more open innovation, more sharing of data, more collaboration in the innovation process between diagnostics companies early on, and also patients getting that input.

The second thing is really this broader collaboration piece, and that's involving reimbursement and regulatory authorities, and crossing geographic boundaries. There's clearly a desire to get more consistent on a global level around how we tackle some of these challenges. I think the

third and final thing comes back to the technology component. I think we are now getting to a stage in the information age where we can really start to tackle some of this big data which is needed to drive personalised healthcare forwards, and we have the technologies to do that in addition to the new biomarker diagnostic technologies which will help identify those patients.

So there's a number of areas where we're seeing exciting developments and I think what has been really refreshing about this discussion is there seems to be, as you described, a real willingness for the pharma industry, patients, regulators, reimbursement authorities, and diagnostics, healthcare professionals, to all get involved and find solutions. So I think we have an optimistic future for personalised healthcare. Thank you all very much for your time it's been a really good discussion.

About the authors



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