WELCOME TO GENOMIC MEDICINE

HOW GENOMICS AND I.T. ARE REVOLUTIONISING HEALTHCARE

DATA SHARING
Heidi Rehm tells us about ClinVar and improving the quality of patient care.

EXCITING TIMES
FoG London keynote speaker, Nazneen Rahman shares the questions she's asking as we move forward.

GOING DIGITAL
Eric Topol, explains how technology and understanding are changing healthcare.
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It’s been an action packed couple of months that have seen the FLG team head across to the USA twice. We headed over to Baltimore for ASHG in October, and then made the trip out to San Mateo for our very own Festival of Genomics California.

I learned two very important things on those trips. 1) Travelling on a temporary passport isn’t as easy as I had hoped, and 2) we’re starting to achieve some of what we set out to do a little over a year ago.

ASHG was a milestone show for us. A year ago, our CEO/Founder, Richard Lumb, and our Commercial Director, Freddy White, made the trip out to ASHG in San Diego on their own. At that time the Festival of Genomics was still a concept that was taking shape, the magazine still hadn’t launched, and our website had been live for a single day. A year later, 7 of us made the trip out to Baltimore. We had our very own stand, and we produced a special edition of the magazine just for ASHG. Not only that, but we’d also already run the world’s first Festival of Genomics in Boston. In a year we’d gone from people wondering who on earth we were, and looking at us with a healthy dose of scepticism, to people coming up to us saying how much they loved the Festival or how useful they find the magazine. Our goal remains the same: to deliver the benefits of genomics to patients faster. Hearing that our events are bringing people together to share their work but discuss how to take things forward is very positive. Hearing directly from people that they find the magazine an enjoyable read and a useful educational tool is heart-warming.

Here at FLG, we’re always thinking about what else we can do. What can we put out there that doesn’t exist already and that you guys will either really enjoy or find useful? As we constantly look ahead, it can be easy to forget what we’ve achieved so far.

In a year we’d gone from people wondering who on earth we were, and looking at us with a healthy dose of scepticism, to people coming up to us saying how much they loved the Festival or how useful they find the magazine.

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This issue of the magazine is one I’m particularly excited about. Heidi Rehm, Eric Topol, and Nazneen Rahman are three people I’ve wanted to feature in the magazine since the beginning. To get all three in the same issue is a bit of a dream come true and the perfect way to cap a great 2015. It’s my favourite issue of the year, and I hope you guys enjoy reading it.

It’s onwards and upwards at FLG, and we’re looking to open 2016 with a real bang. Festival of Genomics finally hits London on the 19th-21st of January. The crowd over in the USA has been great. Their willingness to get involved and be part of the greatest (genomics) show on earth has been really fun. I’m looking forward to seeing how the UK audience brings the Festival to life. If you’re in the area, come on down, make yourself heard, and have some fun!
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This has been a tricky edition of the magazine to put together with so many trips across the Atlantic, but it’s all been worth it in the end. We asked our Twitter followers who they’d most like to see interviewed in a future issue of the magazine. Eric Topol was the popular choice and here he is! It’s a constant surprise just how nice people are, and how willing they are to give up some of their time. As a group, our interviewees and contributors in this edition have been an absolute dream to work with and we hope you find their stories as inspiring as we did!

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**CONTRIBUTORS**

Carl Smith / Managing Editor  
In this issue, Carl got star struck with some very high profile interviews, looked ahead to Festival of Genomics London, and suffered through Victor Frankenstein at the movies so you don’t have to.

Liz Harley / Content Manager  
The second CLARITY challenge took place this year. Liz caught up with co-founder Alan Beggs to understand how the challenge came together and what it might mean for genomic medicine going forward.

Paldeep Atwal / Mayo Clinic  
If you were at Festival of Genomics California you will have seen Paldeep in action as he chaired both days of the Genomic Medicine stream. Here he tells us how Mayo Clinic are making genomic medicine a reality.

Luke Hickey / Pacific Biosciences  
The reference genome has been around for 15 years now, but it’s starting to show its age a little. Luke explains why we need to start building global human reference genomes for diverse populations.
Race The Helix
Runners at Festival of Genomics California get on the treadmill to raise money for Race The Helix.
ACMG AND AMA CALL ON FDA TO RECONSIDER LDT GUIDANCE

ACMG AND AMA CALL ON FDA TO RECONSIDER LDT GUIDANCE

It’s been a little over a year since the Food and Drug Administration (FDA) presented their draft guidance on laboratory developed tests (LDT). The draft was met with mixed reactions, and certainly raised a lot of questions. Unfortunately, the proposed framework would significantly increase the cost of developing an LDT, potentially stifling innovation.

As part of the coalition working with the American Medical Association (AMA), the American College of Medical Genetics and Genomics (ACMG) issued a detailed letter to Congress, the FDA, and the Centers for Medicare and Medicaid Services’ (CMS) Clinical Laboratory Improvement Amendments (CLIA) Program as they work out how best to proceed. ACMG has also been working directly with government and industry stakeholders to work towards a solution.

ACMG’s position on the matter states that any oversight framework must ensure high quality genetic testing remains available to physicians and patients, and that it be able to keep pace with the speed at which new technology and applications are developed.

ACMG’s official position reinforces the importance of accuracy in interpretation of tests, “Genetic and genomic tests are highly complex tests based on recently acquired and rapidly evolving knowledge; they are not tests that produce individualized results on their own but require expert interpretation informed by medical and family histories to ensure their safe and effective use by providers.” ACMG also asks policymakers to evaluate ways to strengthen the CLIA program in balance with determining the appropriate role for FDA oversight.

AMA COALITION LETTER SUPPORTS ACMG POSITION

“The undersigned organizations represent a diverse and broad community of medical centers, laboratories, physicians, and other professional health care providers involved in delivering medical care to millions of patients daily. We stand united in support of modernizing the oversight framework for high complexity clinical laboratory developed testing services and procedures primarily through reform of the Clinical Laboratory Improvement Amendments (CLIA).”

VERITAS GENETICS BREAK $1,000 GENOME BARRIER?

Sequencing an entire genome for $1,000 is considered a crucial tipping point in genomics. Breaking that barrier could make sequencing commonplace, and bring genomic services within reach of the budgets of many healthcare providers. In 2014 Illumina announced the barrier broken by its HiSeq X Ten sequencer. However, this bold assessment has been criticised by some in the community for not including the cost of interpretation. $1,000 would get you the sequence but not the analysis, which at least from a healthcare perspective, is the most vital outcome.

Veritas Genetics announced that they could provide a $1,000 genome and interpretation, to patients through their partnership with the Personal Genome Project (PGP). PGP has more than 16,000 participants worldwide, whose genomes will contribute to research into personal genomics and precision medicine.

“Today’s announcement is a watershed moment that will truly change the way we take care of ourselves and our families,” says Mirza Cifric, Veritas Genetics’ CEO and Founder.

“GENETIC AND GENOMIC TESTS ARE HIGHLY COMPLEX TESTS BASED ON RECENTLY ACQUIRED AND RAPIDLY EVOLVING KNOWLEDGE.”
UK GOVERNMENT ANNOUNCES £250 MILLION FOR 100,000 GENOMES PROJECT

The UK’s 100,000 Genomes Project is set to receive £250 million from the UK Government over the next five years, as part of the 2015 Spending Review and Autumn Statement. The announcement comes as part of wider Government investment in health research and development totalling in excess of £5 billion.

"By 2020 integrated care records will give every health and care professional concerned with an individual’s care the information they need to provide safe and prompt care."

UK science as a whole has also benefitted from the Autumn Statement, with a commitment to protect the annual £4.7 billion science budget. "The government will continue to prioritise investment in science to ensure the UK remains a world class centre of research," the Statement reads.

"Already the UK is attracting more research and development (R&D) investment from abroad than China, Japan, Canada and Russia combined."

George Osborne, explained that this spending is part of the Government’s plan to create a "country that lives within its means", through the use of technology to cut costs and drive reform.

FDA LAUNCH ‘CLOSED BETA’ OF PRECISIONFDA PLATFORM

The US Food and Drug Administration has unveiled a ‘closed beta’ version of their open source cloud platform. PrecisionFDA will act as a community platform where users can share their NGS datasets and benchmark bioinformatic approaches.

In its current form, potential users must request access through the PrecisionFDA website, until December 15 when the next beta release is set to happen. Any group or individual with something to contribute to the platform, such as source code, data or even user feedback, can request access. Kass-Hout noted that initially the focus would be on enabling users to compare data and pipelines against a reference set or data from the PrecisionFDA community.

Following the beta phases, the platform is expected to roll out publicly in March 2016.

AUTUMN STATEMENT

The Autumn Statement is one of two statements from HM Treasury that Conservative Chancellor George Osborne delivers to Parliament each year, the other being the Annual Budget. The Statement usually announces changes to spending plans and changes to national insurance contributions and taxes.
DNA REPAIR CLAIMS NOBEL PRIZE FOR CHEMISTRY

Scientists Tomas Lindahl, Paul Modrich and Aziz Sancar were named the winners of the Nobel Prize for Chemistry at a news conference in Stockholm. Their work on the mechanisms used by cells to repair damaged DNA has netted the winners one third of 8 million Swedish kronor (£634,000; $970,000) each.

According to the Associated Press, “Tomas Lindahl was eating his breakfast in England on Wednesday when the call came — ostensibly, from the Royal Swedish Academy of Sciences. It occurred to him that this might be a hoax, but then the caller started speaking Swedish.”

“It was a surprise. I know that over the years I’ve occasionally been considered for a prize, but so have hundreds of other people. I feel lucky and proud to be selected today,” said Tomas Lindahl, from the UK’s Francis Crick Institute, on receipt of the Prize.

In the 1970s, Lindahl countered conventional wisdom that DNA was stable by showing that the molecule actually decayed at a surprisingly fast rate. As a result he went on to discover a mechanism called base extension repair, which counteracts this degradation. Sancar identified a different DNA-mending process called nucleotide extension repair, while Modrich demonstrated how cells reduce the number of errors that can occur when DNA is replicated.

In a press statement the Nobel Committee explained their decision: “Their work has provided fundamental knowledge of how a living cell functions and is, for instance, used for the development of new cancer treatments.”

2015 NOBEL PRIZES

THE NOBEL PRIZE IN PHYSICS 2015
Takaaki Kajita and Arthur B. McDonald
“for the discovery of neutrino oscillations, which shows that neutrinos have mass”

THE NOBEL PRIZE IN CHEMISTRY 2015
Tomas Lindahl, Paul Modrich and Aziz Sancar
“for mechanistic studies of DNA repair”

THE NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE 2015
William C. Campbell and Satoshi Ōmura
“for their discoveries concerning a novel therapy against infections caused by roundworm parasites”

Youyou Tu
“for her discoveries concerning a novel therapy against Malaria”
INTERNATIONAL SUMMIT ON HUMAN GENE EDITING

All eyes in the CRISPR world would have been on the National Academy of Sciences in Washington in December, as scientists from across the world gathered to take part in the International Summit on Human Gene Editing. Jointly organised by the US National Academy of Sciences, the US National Academy of Medicine, the Chinese Academy of Sciences and the UK Royal Society, the Summit agenda included a debate on a ban on the use of CRISPR to edit human genomes.

The scientific community largely agrees that it is too soon to apply CRISPR/Cas9 to humans. Despite a number of successful animal modifications, it has not been shown to be safe enough to make the transition into humans. Outside of technical ability, there are major questions to be answered on the ethical standing of human genome editing. It’s plausible to think that some IVF clinics may attempt to use CRISPR, as it is not currently against the law in a number of countries including the USA. As the technology develops, big questions need big answers.

CRISPR is the most precise gene-editing technique that we have, but there is still a high risk of the enzyme targeting the wrong section of DNA. Despite December’s announcement from the Broad Institute that CRISPR pioneer, Feng Zhang has honed the technique to reduce the risk of these “off-target” edits, there is still a real concern that editing germ line cells to correct one problem could cause unintended issues elsewhere.

But is banning CRISPR research in human embryos the correct response to these concerns? Writing in Nature ahead of the summit, Jennifer Doudna argued that “a complete ban might prevent research that could lead to future therapies, and it is also impractical given the widespread accessibility and ease of use of CRISPR-Cas9.” She argues for a “solid agreement on an appropriate middle ground,” that allows for basic research, but prevents the use of germline-editing for the creation of genome-edited humans. “The technology and our knowledge of the human genome are simply not ready to do so safely,” she argues.

In a recent leader the New Scientist argued that the impulse to ban even basic CRISPR research is understandable, but ultimately counter-productive. “Possible” is not the same as “inevitable” or “acceptable”. We could clone humans, but nobody does so, because there is an international consensus that it is unethical. Engineering heritable germline DNA could be regulated the same way,” the piece explains.

The National Academy of Sciences hoped that the meeting would identify the scientific, ethical, and cultural differences in how different countries think about genome editing. As Doudna notes, this meeting is the perfect chance for the US, UK and China to lead the discussion, “and for the genome-editing community to renew its commitment to wholeheartedly engage with the public.”

Following the Summit, the organising committee, chaired by Caltech’s David Baltimore, released a statement on the progress made through the meeting. If the main goal of the meeting was to understand the international feeling toward genome editing, then it can be called a success. While we may not have learned anything new from the events in Washington, there is a strong emphasis on continued dialogue both within the sector and with the public at large. This is a positive sentiment moving forward. As the statement says “While each nation ultimately has the authority to regulate activities under its jurisdiction, the human genome is shared among all nations. If the previous communication failures around genetically modified organisms have taught us anything, it is that if the public are left out of the conversation, their trust in scientists disappears overnight. CRISPR, has such huge potential for human health that the community cannot afford to let mistrust and fear rule the discussion.”
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Visit bio-rad.com/info/2016FoG-UK for the publication list and to learn more.

* Based on PubMed data, October 2015.
Let’s Get Digital

Eric Topol, Director, Scripps Translational Science Institute, & Chief Academic Officer, Scripps Health, & The Gary & Mary West Chair of Innovative Medicine Professor of Genomics, The Scripps Research Institute, & Senior Consultant, Division of Cardiovascular Diseases, Scripps Clinic

It’s an exciting time for healthcare. Mobile technology, cheaper sequencing, and increasingly sophisticated informatics are opening up a new era of patient power. The tools are all there, so what’s holding us back?

What can you say about Eric Topol that hasn’t already been said? He’s previously been voted ‘Most Influential Physician Executive in the United States’ in a poll conducted by Modern Healthcare, he’s also been named one of GQ’s ‘Rock Stars of Science’, he’s been known as the Dean of Digital Medicine, and even been referred to as ‘God’ by some of our readers. So it was no surprise, that he topped our survey of who you’d most like to see interviewed in Front Line Genomics magazine.

If there’s one thing I learned about the man during the course of this interview, it’s that his determination to improve healthcare is showing no signs of letting up.

FLG: You’ve been one of the strongest advocates for genomics in healthcare, and a very active promoter of precision medicine. What’s motivating you?

ET: Oh well, I think as a practicing physician for three decades, I’ve been in touch with how imprecise medicine is and how we don’t take into account individuality. We have this new capability that’s been coming online over the recent years. And so to me, these are exciting times in medicine with the ability to have this high definition human being capability that just wasn’t present previously.

FLG: How do you balance the benefit to the individual against the benefit to the population?

ET: We’ve had it all backwards until now, and so whether it’s mass screening for things like mammography or PSA or whether it’s using medications that don’t work in most people- these are very good examples of when you treat people all the same at a population level. On the other hand, if you build from the ground up, it’s kind of like what I would consider, reversed epidemiology. It’s a bit like instead of studying populations from 30,000ft, you’re studying them from granular data of each individual. And you start to understand that the simplistic reductionist notions we’ve had all these years about mass screening or mass drug therapy or mass anything is altogether wrong. I think we can actually build, ultimately, a mammoth knowledge resource that has billions of peoples’ granular data to help improve medical decision making in the future.

So it’s a whole different way to approach the problem. It’s actually defining each individual exclusively and then pooling that data, assuming we can get over the hurdles of privacy and security, and then having such things as a nearest neighbour analysis to say, oh well, this person did exceedingly well with this particular treatment and this outcome and these are your closest neighbours as to your Google medical map, if you will. And it isn’t just genomics, it’s all the different omics, it’s all the different physiologic measurements through censors and anatomical measurement through scans and the environment, the exposome, which we can quantify to a large degree also with sensors.

FLG: Are we giving enough attention to those environmental factors that can impact on large proportion of people? Are we spending enough money to try solve things at the root of some of those problems?

ET: Well I think we didn’t have the tools to do that as well as we do now. For example, we can quantify air quality and, so many environmental hazards through sensors today. Being able to track that along with the natural history of people and for almost everything, there’s some kind of combinations of genetics as well as environment that come into play. And this way we could start to dissect the interaction. So for example if people are exposed to radiation, only a very limited number will develop cancer and why is that? Well, they probably have a genomic susceptibility. Understanding that as an interaction when you can quantify all parts, all components, that’s requisite, just start to really zoom-in on what’s happening.

FLG: There were a lot of people who got very excited around the Human Genome project, who subsequently felt a bit deflated when all of these miracle cancer cures didn’t materialise all at once. Is there a danger of over hyping genomics in the same way?
ET: Well, there isn’t any question that in the year 2000 when it was declared that the human code was cracked, that there was much hype, and expectations were grand. It’s taken 15 years subsequently for us to be in a position where we’re starting to see the fruits of those efforts. The delay here has been substantial but our biggest problem today is we have generated tremendous amount of knowledge. For example, the interactions of drugs with people’s DNA, we understand if they’re going to work and whether there are going to be some very important side-effects. Our biggest problem is now implementing that into practice, into the care of patient. The problem back in 2000 was that we didn’t have that much knowledge, we just had hodgepodge sequencing of the human genome. Now, we’ve had, somewhere around 200,000 plus people’s genomes sequenced and we’ve got a whole lot of studies to understand susceptibility to many different diseases, and we can sequence cancer, we can sequence infectious diseases - but one of the things that we have not really utilized across the board is pharmacogenomics in drug interactions.

FLG: When you moved to the Scripps you launched the Genomic Medicine Program and the Scripps Translational Science Institute to really try and challenge and change healthcare, and take advantage of the new technologies and knowledge coming through. How successful would you say you’ve been in that endeavour?

ET: Well, we’re nine years into it. We are fortunate to get very strong support from the NIH and other significant grantors and philanthropy, in our efforts. You know, we have almost 60 people dedicated working on this individualised medicine theme. We’ve made, I think, some important contributions and hopefully, we have many more to come. For example, we sequenced several hundred people who we called the well-derly –they have an average age of almost 90 and they have not been sick of any significant chronic illness and don’t take any chronic medications and we believe it’s really important to put that out as the healthy genome reference. Albeit, just for European ancestry. We still think that needs to be done for Asian and African ancestry but until now there hasn’t been nearly enough interest in health span genomics. Sequencing a genome is one thing but sequencing people who would serve as a control for most late onset diseases is another matter. So we’ve done that and that took us several years. We’ll be reporting on that very soon.

We’ve had many other projects where, for example, we’ve emphasized pharmacogenomics, and we now have a new program an infectious disease genomics. So, for people who come in with sepsis where the pathogen is not diagnosed quickly, we’re trying to use sequencing to facilitate and catalyse that whole process. Of course the other big thing, is we have not taken the view that it’s all about just sequencing, or biologic-omics.

“WE HAVE THIS NEW CAPABILITY THAT’S BEEN COMING ONLINE OVER THE RECENT YEARS. AND SO TO ME, THESE ARE EXCITING TIMES IN MEDICINE WITH THE ABILITY TO HAVE THIS HIGH DEFINITION HUMAN BEING CAPABILITY THAT JUST WASN’T PRESENT PREVIOUSLY.”
Early on in the program, we started to recognize that digitizing human beings, which is what sequencing is one component, one element of that, but that means also using sensors and other tools to get this data about each individual because you can only get so much out of a sequence. So, our efforts have been to try to use as much many of these different layers of information and integrate those layers to define each human being from a medical assets point of view.

**FLG:** How do you go about pulling in all these different kinds of data sources, managing the data in first instances and then actually having, the sophistication to work across databases and pull it all together to come up with applicable findings?

**ET:** Well, if you look at the largest component of our group it’s the bioinformatics team. It’s an effort led by Ali Torkamani who’s really quite a wizard and a brilliant informaticist and the others including Andrew Su and we also work with the San Diego Supercomputer Centre. This data is not just big but it’s also thick because there’re many layers. And it’s also long data because it’s longitudinal in many cases, for example when you have sensor data at many points in time. So, it’s a challenge and is the grand challenge for us in medicine going forward. Not only being able to integrate all these data but being able to translate what it means for the patient, the individual and also for the doctor who’s looking after that person. 23andMe, one of their greatest contributions was that they did a really good job of educating people about their genomic findings. They had really simple diagrams and they could make things that were previously very hard to explain readily understandable for the vast majority of people. And that’s also important for doctors who largely don’t have such a good grounding in genomics. So, it’s not only interpretability of the data but also distilling it in a way that is eminently understandable.

One other point which I think deserves emphasis, we live in the land of VUS, Variants of Unknown Significance. And we’re not going to clear that up for years because we need millions and millions of people sequenced with phenotyping and ideally not just do they have a disease or not but much more depths of phenotyping. So, we are in a suspension right now because so much of what a genome sequence will get us today, it lacks being informative. We can see a way through that and in a few years when millions of people are sequenced, if those data are all pulled together we’ll be much smarter and it will be so much more valuable to have a genome sequence.

**FLG:** Yes, right. Data is kind of an interesting question. I think one of the things I tend to ask people is what they feel some of the biggest challenges are in integrating genomic technology into healthcare. A few tend to crop up quite a lot, mostly education, in terms of educating the public and educating physicians, and data is another one. Right now we’re in the situation where there are so many different projects going along different initiatives that you have all these little pockets of data, which is great on one level. It shows that lot of people are doing some great work here but it’s gotten to the point where it would be even better if all of these databases could talk to each other a bit better.

Is that something that you’re working towards or something you think is important or just kind of whoever gets there first owns it?

**ET:** No, I think that we have to get over that mentality. That’s why I joined the board of directors of the Sage Bionetworks because they’re really pushing the open science agenda. I think we need open science, we need open medicine, we have to really change the culture because we’re only going to get there faster if we share the data and we work on this, as a biomedical community. We can’t continue to publish, owning data and sequestering it from one another. Now that’s just turned out to be a big grand obstacle to getting where we need to be. And here we’re talking about the power of numbers, we’re talking about the crowd interpretation of that data too by the wisdom of the crowd. We have to change and adapt. Medicine has been behind some other communities like physics and mathematics and even biology, but the medical side has to follow suit that data can be eminently shared today. The only way we can help people more in the future, is to do that. It wouldn’t be acceptable any longer for us to continue sequester data in particular health systems and research environments and companies even. This is going to be real difficult thing to justify over time.

**FLG:** What are the series of events you’d predict to take us from where we are now where we have quite archaic or outdated systems, certainly for healthcare and to a certain extent research as well, and what do you see as those key turning points that will take us into this true system of personalised medicine?

**ET:** Yeah, well, archaic is the right word. We have tremendous a problem with paternalism in medicine and we have squashed the patient consumer ability to get to their data and to own it and that has to change. What’s really kind of interesting is that we have this irony of patients taking charge of their data and at the same time of it being a more complex set of data potentially than ever before. Because patients are going to be generating their data from the standpoint of smart phone sensors that can capture any metrics to pre-empt conditions in the future, like an asthma attack or serious depression or epilepsy, seizure. We have this new found ability to capture data where it is algorithmically interpreted. It can be machine-learning for each individual and a virtual medical coach through a smart phone. A lot of physical exams could be done by oneself through a smart phone with attachments. This is an uncanny cluster of new capabilities which is centered on this phone which is of course not really phone, it does so much more. It changed our lives and now it’s going to change our health and medical lives.

At the same time, the medical community is not really into that. In fact, it largely has dismissed the patient’s ability to generate data, claiming it was not accurate or worth much. So, we have real tension now and then superimposed on that are things like being able to get one’s whole genome sequence and, get environmental biosensors and all sorts of other things that are coming into play. So, it’s a very interesting time. It’s kind of a time of data and information overload, and somewhat short on knowledge and wisdom.

**FLG:** What are the implications of generating so much data? Who actually owns it and what kind of risks are we open to?

**ET:** That’s a really good point. My concern on all this is security and privacy of the data. The importance of that has been →
diminished outside of medical circles. Here it's unquestionable that that's a deal breaker if you will, that you can't go forward with this unless we can assure that each person's data are secured and that privacy is maintained. Obviously, it can't be guaranteed 100% but it needs to come as close to that as possible. Today, we're doing nothing to safeguard one's data. One of the most impressive ways we can do that is to help people own their data where it's distributed in units of one or units of a family rather than in millions of people where it becomes a magnetic attractant for hacking.

Beyond that the issue of private security has to be taken seriously because even though one could identify someone from a sequence, the effort required for that is unlikely. I have a hard time thinking that people don't have better things to do than try to understand whole genome sequences that are no way connected to that individual. We'll see how it all plays out but we have to do it far better. We have far more hacking of electronic medical data than we have anybody even accessing their data today.

**FLG:** Although it would take a tremendous effort for someone to try and steal someone's sequence and try and fathom anything from it. I suppose until it happens, we won't really know why someone might wish to go to all that effort. I get the impression that maybe it's going to take that first landmark “Well, this has gone wrong” moment to realise where some of those holes are in terms of dealing with privacy here?

**ET:** Right, right, exactly. You know, I completely agree with you.

**FLG:** In the US you've got a system where healthcare really is a business and can be extremely expensive for the individual. Direct to consumer tests could potentially encourage people to take some interesting preventative measures and really manage their health a lot earlier-on?

**ET:** You know it's interesting that you bring it up here. I had a dinner with Jeremy Hunt (UK Secretary of State for Health) and we talked quite a bit about this. The US, as you point out, there's some small efforts of direct to consumer but it's actually not received very warmly by the medical community. Things like 23andMe or people ordering their own labs…it hasn't gone all that well, to put it mildly. It's especially an exciting time, the likes of which I've never seen in my three decades of practicing medicine.

I think that we can get to a highly intelligent, and really new, plan of medicine. It does invoke shifting more responsibility to each individual and democratising medicine. I think that's a good thing, if not for everyone. And certainly in five years everyone won't be there but now, it's about getting your data that you generated and using software to interpret that data for you. For example doing your cardiogram or doing the ear exam of your child with a possible ear infection or looking at your sensor data from a night of sleep, to see whether or not you have sleep apnoea. All these things today can be not only generated by a patient but also interpreted with algorithms. And then the contact with the doctor is about, “How do I get treated? And by the way, doc, you know what do you think of this data? Does it look all right?” So it's oversight of the data when the doctor's wisdom and experience comes into play, guidance purposes. In the UK and other parts of the world, this does not challenge reimbursement. This does not really create a problem. If anything, the only common problem is that doctors don't really want to lose control, and that's the same everywhere. But other than that, at least the financial implications are much less outside the US. So there's a chance that many of the things that we're talking about could take hold, where the incentives are not based on the fee-for-service type system that we are still stuck with in the US.

**FLG:** Looking at precision medicine what would you hope it looks like in let's say 5 and 10 years time?

**ET:** Well, the hope is that each person would have the requisite data for decision making. Is it going to get a new drug prescribed to know that it's actually going to work, that they're not going to have some serious side effects? If they're going to have a screening test that they know that they really need it? Or this is a wrong turn in their life? And basically if they are susceptible to certain illnesses that they know it very early in their life that they adjust their behaviours and their nutrition and all the things they can do to pre-empt that illness from ever striking.

I think that we can get to a highly intelligent, and really new, plan of medicine. It does invoke shifting more responsibility to each individual and democratising medicine. I think that's a good thing, if not for everyone. And certainly in five years everyone won't be there and we'll only partially get to that point. But I think it's attainable and it's especially an exciting time, the likes of which I've never seen in my three decades of practicing medicine.

**FLG:** As for those of us working in and around genomics what parts should we be playing to bring that change about?

**ET:** The biggest thing we can do right now is pool efforts. So, in cancer there are a lot of people getting their tumour sequenced. More and more people are getting their circulating tumour DNA in the blood sequenced and that data is not all being aggregated and we're not learning collectively from it. Right now the biggest problem we have is, we're starting to use the tools but we're learning and we're not translating that into medical practice. That has got to get accelerated. We've got to have a new attitude and willingness to do both those things: sharing of data and implementing the new knowledge into medical practice.
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From speaking at Wired, to being featured in the Financial Times – if you're reading this you probably already know who Nazneen Rahman is. But in a field full of brilliant minds, what makes her such a compelling individual? Despite having a remarkable career working on cancer, it's rarely the subject people want to draw her on. It's always the 'big questions'. As a self-confessed technophile, she has an amazing ability to quickly see where new opportunities might come from and how to make the most of them.

Ahead of her hotly anticipated appearance on the Festival of Genomics London main stage, we were thrilled to get a preview of what to expect.

FLG: You have spectacular research career, you've been pretty vocal in campaigning for and promoting various issues, and you have an album out as well...

NR: Yeah, my other life, which was a secret for a long time, but it's no longer a secret. You can't have secrets in the modern age!

FLG: We've been pretty impressed by it in the office! Well, our first question has to be- how do you find the time to do so much?

NR: Well, for a lot of my career, I've been a really very hardcore scientist and really taking new technology and trying to use it - sort of use it to destruct as much as one can to make new discoveries and translate these into the clinic. I'm a technophile actually going through all the things that I do including the music in fact. I'm an early adopter. I'm interested in anything new really, whether it's in the social dimension or not. I like new things and genomics just has turned out to be something where there have been such extraordinarily, transformative, and disruptive new innovation. That's been really interesting to me. I've also been very interested in global connectivity, and how that's allowed one to influence, interact and make an impact on scales that just weren't possible before. In some ways, exploiting that global connectivity which to my mind is just a new method just like sequencing is a new method, is equally disruptive and transformative. I'm sort of a serial innovator in many ways, an entrepreneurial sort of scientist and doctor really.

The music has also been about the technology. That's made the difference to me. 20 years ago when I was in college - if you wanted to do music, you had to get a band together. It was a big organisational sort of enterprise. I really got back into music through technology. My album has got lots of different types of instruments, most of them are computer generated because you can just do amazing things which sound extraordinary. I love sort of layering on vocals, that's always been a real thing of mine but that's really easy to do in the modern age. Technology allows you to just be incredibly more productive with less time really. So I think that's been the core of it really, adapting all of these new tools. I love productivity tools.

FLG: Working as a doctor and scientist must give you an interesting perspective on how you go about your work in both domains?

NR: Well, for a lot of my career, I've been a really very hardcore scientist and really taking new technology and trying to use it - sort of use it to destruct as much as one can to make new discoveries and translate these into the clinic. I'm a technophile actually going through all the things that I do including the music in fact. I'm an early adopter. I'm interested in anything new really, whether it's in the social dimension or not. I like new things and genomics just has turned out to be something where there have been such extraordinarily, transformative, and disruptive new innovation. That's been really interesting to me. I've also been very interested in global connectivity, and how that's allowed one to influence, interact and make an impact on scales that just weren't possible before. In some ways, exploiting that global connectivity which to my mind is just a new method just like sequencing is a new method, is equally disruptive and transformative. I'm sort of a serial innovator in many ways, an entrepreneurial sort of scientist and doctor really.

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I'm bit of a doctor and a scientist- I run a clinical unit of making the discoveries, making impact in the clinic, but also the things that we decided to work on are very influenced by the problems in the clinic. So I have that sort of circularity that's allowed me to go between them, and make impact in most of those areas.

FLG: Yes, I think sometimes it does, sometimes it doesn't. Often the sort of science I've done has essentially been about puzzle solving. There are things that are perplexing, or which aren't solved, and one has the potential to try and find answers. That's often the driver. It's a relatively pure, sort of, wanting to just try and discover new things. →
"When the general public come into contact with genetics in a healthcare context, they are confronted with results in terms of percentage risk. As a doctor really, how do you go about explaining to patients what the concept of risk is and actually still get them to appreciate the importance of genetic research?"

Nazneen Rahman, Professor of Human Genetics, The Institute of Cancer Research & Head of the Cancer Genetics Clinical Unit, The Royal Marsden NHS Foundation Trust

Professor Rahman’s research work has been directed towards mapping and identifying human disease genes, with her primary areas of research being breast, ovarian and childhood cancer susceptibility, and studies of human overgrowth. She also has a strong commitment to translation of research and is currently leading a translational research programme which aims to introduce testing for cancer predisposition genes into mainstream oncology services.
It’s certainly true that the things one tries to address are very much influenced by the patients one sees. One does understand the systems better but one also does have the authority to be able to do that. And I think that there are many, many, many scientists who really find it very important to do research that can potentially have a positive impact on human health. But they find a way in which they are trying to make that happen is a little bit indirect, they have to go somehow through the NHS in the UK which is, you know, an ongoing mystery to everyone including those of us who’ve been in it. I’m trying to change myself; I’m changing at least my own practice, so it should be at least one degree easier than changing somebody else’s. So, I think that can be really, really helpful, yeah.

**FLG:** NGS has been a huge disruptive technology. Is it having the impact that people thought it would?

**NR:** At the research level, it’s having an impact bigger than my wildest dreams, and I do dream pretty wild. It’s just been extraordinary. I never thought I’d be able to do the sorts of things I can do now because of NGS, in my career. So the research capacity, it’s been extraordinary. And in a clinical capacity, it’s less. When you’re doing genetic testing, there are a number of different things that have to be at the clinic. For a long time, the genetic testing was the bottleneck. But it’s moved it elsewhere in the pathway. Getting samples from patients, to NGS, to getting your analysis, to getting your interpretation, to going back to your patient to give that information or the action- that’s actually a long pathway. And it’s actually moved the bottlenecks to other parts of those pathways. In the clinic, all the parts have to work, otherwise nothing works really. So that’s what’s challenging in the clinic. And also in the clinic, you’re always dealing with people, and people are always difficult to deal with. They don’t respond to evidence. There are all sorts of things that you have to address when you are dealing with people in a way that you don’t on theoretical side.

**FLG:** The stuff that we hear most frustrations on, here in the UK, is that we don’t quite have the system or infrastructure in place to really make the most of genomics in the NHS.

**NR:** Yeah, so I’m sort of more optimistic about it, I think it does involve more radical change than is happening. I think one of the things that has been a factor here that’s pretty unusual in that sense, is the degree of the change. I’ve never come across it in my career. Usually things change iteratively, and so you have a bit of time to accommodate in the process, as the technology or whatever is also progressing. Here we didn’t have an iterative change at all. It was a completely different kind of change. So, it’s very, very radical transformative change.

I often use transport as an example. So previously we were sort of doing this journey of genetic testing as if we’re sort of hobbling getting from A to B, and then suddenly we could go by rocket. So, that sort of degree of change. And on the one hand, you’re thinking, “Oh, it’s great, you can go by rocket now”. But it depends. If you’re doing a very short journey, if you’re trying to go from Leicester Square to Covent Garden, actually trying to go by rocket is causing you all sorts of extraordinarily difficult problems. You’d actually rather have a bike, or the tube or something. What people have tried to do, which I think is doomed to failure, is they’re trying to sort of upscale the previous systems. And that cannot work. You’ll have to have an equally radical way of doing all of the surrounding aspects about it. I think that is possible in some of the things that we’ve been doing.

One of the things genetics has always done, we’ve always been about sort of edge cases, the 0.01% rare cases. Everyone in genetics was kind of drawn to it because we like that sort of thing. But what we need to do is automate. You have to do that because we’re talking about an average 20,000 variants per exome, more if you’re looking at a genome. Well, most of those can be automated. There are always going to be edge cases and they’re going to need special care. But what we need to do is have completely radical new systems to match the radical sequencing that can deal with that, sort out ones that can go straight to the system and then put specialized focused attention to the very, very small proportion that’s going to need that.

We do need to accumulate much more information about the normal population- the baseline variation. We are missing lots of bits and pieces of data that we would have got if we had a more gradual change to this process. But I think the fundamental thing is, it needs a radical change in thinking.
FLG: Getting more people to share their data and work collectively to address inconsistencies in interpretation should hopefully help ease the integration into healthcare with more confidence right?

NR: I think it will help solve the problem. The approach has been very one dimensional and individual variant based. We’re not collecting the denominators. People will upload their variants but actually what we want to know is how many sequences did you do and how many times you see that out of all the sequences you’ve done. We typically haven’t got that clinical context. Context is always incredibly important and often underappreciated. So, even in some of the most classic genes like, for example the BRCA genes people assumed that if you have a particular variant that it always gives same the risk but it doesn't. The risk of cancer is very variable, it can vary from 30% right the way up to 80%. There are big changes in risk depending on other factors going on which we don't know about yet. What we can see observationally is that you have strong family history, but sometimes you have no family history. That actually has been one of the disappointing aspects of genomic medicine. The amount of prognostic information we can give to patients is very limited.

What we do know is that the impact on that person can be very, very variable even to most classic sort of Mendelian diseases. What is causing that partially will be chance, but also lots of other factors are going to play there that we've only really got a surface understanding of. All of that is fine except for the problem where people are doing much more population testing and saying, "We found this so called incidental finding and therefore such and such happened", and they're basing their recommendations on information imparted from people with strong family history or an extreme phenotype and then they're extrapolating that into the general population. But we absolutely know that that isn't appropriate.

FLG: A lot of the general public understand that genes can have strong causative effects, but can sometimes get caught up in thinking that a particular trait, or disease, is caused by a single gene variant. However, when they come into contact with genetics in a healthcare context, they are confronted with results in terms of percentage risk. As a doctor really, how do you go about explaining to patients what the concept of risk is and actually still get them to make decisions on the basis of numbers. And if they do, it's really very ballpark, you know, if it's over 50% compared to under 50%, there's got to be a different threshold. But I've never met anyone who was able to change their decision based on whether the risk was 70% or 80%. So, I have much more of a discussion if the threshold is wide, or if the threshold is somehow going to impact their clinical actions. Say one of the classic things we talk about in genetics is about the set of conditions you've got. In the case of cystic fibrosis you might have a couple who are carriers. And you'll say to them it's a 25% risk of having a child with cystic fibrosis. Some people say, "Oh, my god, that high?" And some people say, "Oh, that's, that's quite low." You can sort of, predict which way it'd go, but you can still get surprised. People, sort of, prism on how they're thinking about it. And actually what decision they make is mostly affected by two things: whether or not they've got children. If people have children, they'll do anything and just want to be alive for their children. And whether or not one of their parents suffered from the condition. If they've had a condition and they survived and they were treated and fine, they will - that will have an even influence compared to people who lost their parents when they were children. So, it comes down to really, quite understandably, an emotional type logical.

I'm very in favour of science communication but with the plethora of media outlets and the need for headlines, you get re-simplistic headline information. But I think that has made people become pretty sophisticated about it because they just so deluged. One minute, something's causing cancer and the next minute, it's not causing cancer, and you've got these genes for this... 20 years ago, when I a junior doctor, whenever anything came out in the press that was having something to do with cancer or a particular treatment, I knew I'd be up all night on call because people would be calling and saying, “Can I have the latest treatment?” No one ever calls us now because they think, “Yeah, yeah, they can't all be true.” Which actually, sadly, is the appropriate response. I think they realised finally, for tragic reasons, that it has to be more complicated than the way that that is being portrayed to them.

I think the understanding of risk is really, really, just genuinely very, very complicated for all of us as individuals and as societies. Particularly with things that might happen in, or might not happen, in the future. We're just terrible at making good judgement from that and there are all sorts of biases in there that are both conscious and unconscious and we're just really not very good at it as humans, at accurately doing that.

FLG: Definitely! Going back to the willingness of patients being keen to be part of research projects. How can we make those patients feel more like valued partners rather than an anonymous data point?
I think the citizen side of participation is really something to really foster as much as possible. In terms of providing a sample for research, I didn't really get a sense that people feel that they only want to do that if they're involved. But in terms of that participation, the thing that we really need comes back to that sort of prognostic information. Really what we need is really good phenotypic information and longitudinal information. Historically, that was just really low-scale and really ineffective. You'd have to have a doctor or some kind of sort of professional, going to measure or talk to a patient and then inputting that data into a database, etcetera, and it's just terrible. Whereas we get all these people now who are effectively chronicling their lives on Facebook, on Fitbit, or whatever. And if they want to do it, and we need the data, cut out the middle people. That's the way that I think we should be really engaging people in research.

FLG: You raised an interesting point there around data sharing. There are concerns around private companies and genomics start ups and groups like these that are amassing large amounts of genetic data for their own commercial use effectively, that they perhaps don't have any plans to make publicly available. And I'm interested to hear how you feel we might be able to strike an effective balance between being as open as possible with the data that we collect, but also encouraging the sorts of commercial opportunities effectively making a beneficial operating environment for both academia and industry within the genomic space.

NR: I'm very in favour of open data. I'm not very concerned about privacy. I'm not sure why and it feels like there is no privacy anyway and this is the least of one's concerns in many ways. I do think that the balance about the benefits of sharing data compared to the theoretical harms have not been at all balanced. People just don't hear about the benefits as much, or they assume they're happening. The interesting thing about the commercial side, is that these things have to be sustainable. Some of these companies are offering testing at a much reduced price because they're planning to effectively sell those data. I think if people are transparent about it when you're singing up to it and that's what you're getting. That's not very different from many, many other aspects of commercial things that are happening.

Transparency and just being clear about what one is and is not doing I think is really helpful. People don't like to be surprised, and they always feel suspicious and feel a bit aggrieved if they're surprised. But if something's happening that's expected, however awful, sometimes, that's better than if they were surprised by something they weren't expecting. So I think just being transparent and just being clear really is very, very, very helpful.

On opening out data I think there are all sorts of different models to federate data, and keep it safe. I think it's a much bigger thing then just genomics. This is something of our age that we are having to be cognisant of and to engage in. But I think one of the main things that I think haven't been said very much is the benefits of sharing data, we only hear about the negatives. So, I don't think people are really making an informed choice about those things. So, I think, you know it's always easier for people to be sort of very vocal about things they don't like; it's very hard to be a fanatical liberal. But we somehow have to make that happen, I think, because I don't think it's a very even discussion really.

On the commercial aspects, and just making sure you've got sustainability there, and I think that is something that we're going to have to think about in sort of innovative. Often, it can be a win-win. Often sharing those data doesn't inhibit one's commercial model. Usually, data is cheap in all sorts of ways, so actually having any kind of commercial model that's involved in restricting data in that way, I don't think has much legs as a commercial model. I think you had to have some kind of added value of how you're using that data.

FLG: I'm looking forward to hearing more on all of this at Festival of Genomics London in your presentation, 'Implementing Genomic Medicine: Are we answering the right questions?' What do you hope people will take away from your presentation and what are you looking forward to at the festival?

NR: It's sort of interesting you've given these titles ahead of time then you get to writing the talk and start thinking "Why did I give that title?" But I think here it will touch on some of the things that we've been talking about here in terms of, are we really stepping back and thinking, what are the things that we need to address, and are we addressing those in the right way?

So what I'd really like to hope is that the audience will come out of it thinking about genomics in a slightly different way. We're running to stand still, or in fact, running to go backwards because we've been deluged with data, deluged with new things. So, one can often feel like one's sort of fire fighting in terms of implementing genomic medicine. I try and use talks as an opportunity to get information from people. One of the things about the talk at Festival of Genomics is that it is supposed to be sort of fun and felt a bit more innovative. One of the questions I keep asking people is, "Would you like to have your genome sequenced?" And it's quite interesting what people say instantly, and then what they say after my talk. So, in terms of the Festival of Genomics it's getting a bit of a snapshot of these sorts of opinions. So yeah, I'm at that creative science interface, so I'm very interested in all of the slightly creative ways of looking at that question and engaging with people.

FLG: Thank you so much for your time. We look forward to seeing you in London. Is there anything else you'd like to mention to our readers?

NR: It's a hugely exciting time and potentials are huge. I think in some ways, it's always difficult. One wants people to be really aware of that excitement but at the same time it's really beholden on us to be really realistic about why we're excited and the prospects.

Sometimes the one liners that come out are so sort of out of the park that people end up being disappointed and ask "Haven't you done that yet?" I hope people aren't starting to become jaded. I'd become a bit worried that people have become jaded about genomics. But it really is extraordinary opportunity. I mean it feels like genomic technology, informatics, the internet... all of these things all happening at the same time gives us real opportunities and has huge impact on a global level. It's a real privilege to be part of it and we're all part of it.
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After the first human genome was sequenced in 2003 there was a great deal of anticipation and excitement. The vision was of a new era of ‘Genomic Medicine’ where the complexities of a patient’s DNA would be used seamlessly and integrated with current medical treatment. However there were no immediate or tangible benefits apparent, and while the media storm died down, genetic research increased exponentially. Fast forward to today and there is lots of talk of genomic medicine and the new field of precision/individualized/personalized/stratified medicine has emerged promising better clinical decisions through improved individualized approaches. Some of the benefits include better targeted therapies such as molecular targets in cancer, reduced side-effects of drugs with the help of pharmacogenomics testing, increased prevention of prediction of disease using a molecular approach, reduce healthcare costs and improve overall patient care outcomes. Indeed genetics and genomics is reaching an inflection point in terms of cost, volumes and knowledge. The numbers are impressive, cost of sequencing is now below $1000, number of sequences performed to date reaches into seven figures and validated single-base variants in the human genome continues to increase with ever expanding genetic knowledge. Genetics and genomics is firmly within the public spotlight, from direct-to-consumer testing including carrier testing for reproductive risk, genetics of common diseases such as heart disease and obesity, ‘clues’ for conditions such as Alzheimer’s and cancer, all the way to how genetics effects human longevity.

A common analogy used in Genomic medicine is that we are moving from the anatomical microscope, used for centuries in traditional anatomical medicine practices, to the genomic stethoscope. Whilst sounding impressive, the challenges faced with making this transition are considerable.

The Center of Individualized Medicine (CIM) at the Mayo Clinic is the culmination of the needs and desire of one of the oldest and best known names in healthcare effort’s to lead the effort to rapidly translate advances in genetics and genomics into advances in patient care. There are significant barriers which continue to hinder assimilation in mainstream medical practice. Examples include access to and standardization of technology,
education, reimbursement, regulation, evidence-based clinical validity, and evolving ethical dilemmas. CIM is a ‘hybrid’ centre with clinical, research and education responsibilities and its goal is to promote rapid translation of research into personalized clinical care and to create genomic medicine mechanisms that are instantly diffusible and applicable across Mayo Clinic’s multiple, geographically dispersed campuses. One of the main initiatives to accomplish CIM’s goals was the creation of the Individualized medicine (IM) clinic. One unique feature is that, in contrast to traditional academic medical centre models, the IM clinic is not housed within any one established department. A working group was created for the clinic, which includes clinicians across the institution’s departments to contribute expertise. Unaffiliated, the IM Clinic processes were created de novo and designed for the ideal patient encounter, transcending the limits of a single medical, surgical or pathology specialty. Translation programs were implemented, these include specialty areas of microbiome, epigenomics, pharmacogenomics, biomarker discovery and clinomics (Clinical application of ‘omic’ platforms). To support these translation programs, infrastructure support programs such as institutional bio-banking, genome sequencing, and bioinformatics infrastructure, along with a subset of information technology and bioethics resources, were aligned under CIM to facilitate infrastructure coordination and prioritization. As an example the Mayo Clinic biobank has over 50,000 patient samples, a number which is increasing daily. Patient samples have DNA banked and linked extensive electronic medical records which on average contain 14 years of health information. Plans are being actively discussed to perform whole genome sequencing, metabolomic profiling and other ‘omic’ platform analysis and make this de-identified information available to researchers with the hope and promise to improve healthcare across specialties.

**CLINICAL OFFERINGS**

Genomic influences on cancer are well established and molecular characterization of tumours has been shown to be beneficial to patient care and is rapidly becoming the standard in treatment of somatic cancer. For this reason the first ‘service line’ created was for patients with advanced cancer who have failed standard therapy (or where no proven standard therapy exists). The IM clinic uses next-generation sequencing for comparison of normal and tumour DNA to identify causative or contributing mutations and, subsequently, allows targeted therapy based on genomic information.

The second service line created was for patients labelled a ‘diagnostic odyssey’. These are patients with a suspected genetic condition for whom previous testing did not reveal a causal etiology. Often they have had a litany of prior testing and have been searching for a unifying diagnosis for years, and sometimes even decades. Clinical Whole Exome Sequencing (WES) is primarily employed to reveal the variant(s) responsible for the patient’s disease and proposes potential treatments although other more traditional genetic testing such as gene-panels, chromosomal microarray and biochemical genetic analysis are also employed. Additionally more novel clinical strategies such as global metabolomic profiling have been shown to help get a successful diagnosis for patients.

The third service line is called ‘predictive genomics’. This was created due to the increasing demand of patients wanted educated about their genomic data and potential influences it may have on their health even with no apparent disease or traditional ‘clinical question’ to address. Patients will meet with the clinical team and discuss options from a simple family history, often called the first genetic test, to whole genome sequencing. So called ‘intermediate’ options include pharmacogenomics profiling to inform prescribing and testing of ‘medically-actionable’ genes such as the ACMG 56-gene panel. Predictive testing is typically not covered by medical insurance at this time so patients pay out-of-pocket for this testing. The information received from testing is given to the patient and also, where possible used to improve their care plan. For example, once patients undergo pharmacogenomics testing this information is implemented into their electronic medical record in the form of ‘drug-gene’ interactions. To date over 3300 alerts have fired and over 3000 positive findings have been added to electronic medical records. These drug-gene interaction include poor response to medications such as clopidogrel which may be important in the common healthcare scenario of coronary stenting after a heart attack. Indeed this prescribing guidance on clopidogrel is recognized and advised by the FDA yet is still not routinely performed in clinical practice. We hope that through predictive testing and implementation of the data into the medical records, patients will enjoy lower health care costs and better quality healthcare through potential lower diagnostic complexity and appropriate prescribing of medication.

While each service line requires a slightly different work flow and professional skills, a common infrastructure was built to accommodate the basic IM Clinic function. Representatives from IT, bioinformatics, bioethics, patient access management, education, revenue cycle, operations and the research sequencing facilities joined the IM Clinic Work Group to design the structures and processes implemented across all Mayo Clinic campuses. Each patient is given a lead physician who coordinates their care, and this physician acts as their IM clinic consultant. The lead physician depends on the primary reason for referral to the IM clinic, for example in advanced cancer it is often a medical oncolologist or hematologist and in diagnostic odyssey it is typically a clinical geneticist although any specialist such as cardiology, rheumatology and so on can be the lead consultant.

A key component of the IM clinic and one that helps facilitate the patient journey is the genetic counsellor.
Genomic medicine is a complex discipline, vocabulary alone can overwhelm patients however they must be informed about the potential risks and ramifications created by genomic data and genetic testing and so the role of the genetic counsellor is critical. A consultation with IM clinic typically will start with a genetic counsellor who takes a detailed history which includes the construction of a family pedigree and assessment of risk based, inheritance patterns and possible disease origins. Dedicated time is necessary for face-to-face visits between the CIM genetic counsellors and the patient (and often family members). Genetic counsellors define and explain vocabulary and concepts; talk explicitly about different lab tests and their potential results and risks; and apply a shared decision-making model to help the patient select the categories of genomic results to be returned. The genetic counsellor consults with the lead physician and together a treatment plan is discussed with the patient. Given the vast and highly complex nature of genetic testing a post-test expert review board is required for each service line. For advanced cancer, the ‘Genomic Tumor Board’ meets to discuss individual cases and gathers a consensus opinion on interpretation of results and modification in medical management. Similarly, for diagnostic odyssey cases, the ‘Genomic Odyssey Board’ acts as the clinical interpretation team. These expert boards are multi-disciplinary and encourage wide participation and exchange of experience, drawing genomic medicine experts from across the institution, including standing members from Anatomic Pathology, Molecular Genetics, Clinical Genome Sequencing Laboratory, Clinical Genetics, Hematopathology, Medical Genome Facility (research), Bioinformatics and Biomedical ethics.

DISCUSSION

There have been many lessons learned since the IM clinic opened around 2 years ago. First patients are coming to us with some genetic knowledge, and with a high-risk tolerance, when it comes to genomic findings. However, even well-educated patients require thoughtful conversations with genetic counsellors and genome-educated clinicians. We also learned that patients want materials ahead of time and materials to take home with them. Electronic education opportunities need to be further explored. Another major issue in conducting genetic testing is that of insurance coverage. Billing codes for genomic lab services need to be established and recognized by payers such as testing is that of insurance coverage. Billing codes for genomic lab services need to be established and recognized by payers such as insurance companies and Medicare/Medicaid. It is often difficult to anticipate what out-of-pocket expense patients might incur and what revenue impact it may have on CIM.

For patients with advanced cancer we are able to find a sequencing-based druggable target around 50% of the time. It is important to note this does not translate to finding a cure and also does not mean the patient will always be able to get additional therapy as clinical context, drug availability and control issues need to be addressed. For patients on a diagnostic odyssey around 30% of the time we are able to find a definitive diagnosis. The question is often posed, why is it not 100%? The reasons are complex, for example the current clinical standard is whole exome sequencing. It is widely regarded that around 85% of disease causing variants are found within the exome, of course this leaves open the path for clinical whole genome sequencing to find other causal variants not present in the exome. The sequencing itself however is also not complete, with difficult to sequence regions, pseudo-genes, copy number variations such as deletions/duplications and triplet repeat disorders which are not reliably tested for on whole exome sequencing partly due to current short-read length technologies employed in NGS. Exome sequencing is improving however, and newer methods such as read-depth analysis and longer-read lengths are improving sensitivity for example for copy number variations, although in the clinical context it does not surpass the gold-standard of more traditional approaches such as exon-level microarray analysis.

Furthermore there are other causes of disease not captured with clinical exome sequencing: post-genome modifications such as alternative gene splices transcripts/isoforms, post-transcriptional modifications, gene fusions (e.g. BCR-ABL) and pathogenic variants which change gene expression are simply not detected on genome sequencing and ‘Whole transcriptome sequencing’ or RNA sequencing. RNA sequencing is tissue specific, dynamic and has the potential to ‘inform’ genomic data such as analysis of expression levels of genomic variants in cancer. Other ‘genomic considerations’ include long-range genome effects such as locus control regions far upstream of gene of effect, cis/trans acting elements, the genetic handicap principle which states that deleterious variants can be ‘tolerated’ if the overall deleterious variant load is low and lastly multi-genic or gene-gene interactions. Clinical testing of these areas is still very much in the early stages and it is exciting to think of what discoveries and advances will be made in the next 1, 5 and 10 years. Given the rapid pace of advancement it is also impossible to predict or know what is next particularly with the advancement of gene-editing technologies such as CRISPR/CAS9.

To summarize, clinical whole exome-sequencing will remain the mainstay of testing in the IM clinic for the time-being, it will evolve as genetic knowledge / analytics improve. New platforms and technologies will translate into clinical practice out of the research realm, and we will use many –omics platforms concurrently to aid and augment the genetic data. As with anything in healthcare all these exciting developments will need to get round the very real challenges of cost, insurance coverage, turn-around-time, education and desire from healthcare institutions.
INTERVIEW

IMPROVE THE QUALITY OF PATIENT CARE BY SHARING YOUR DATA

Heidi Rehm, Director of The Laboratory for Molecular Medicine, Partners Healthcare Personalized Medicine, & Associate Professor of Pathology, Harvard Medical School

WANT TO SUPPORT CLINICIANS AND LABORATORIES WITH THE MOST ACCURATE UNDERSTANDING OF GENOMIC VARIATION AND GENE-DISEASE RELATIONSHIPS? THEN START SUBMITTING YOUR VARIANT INTERPRETATIONS!

Earlier this year, Heidi Rehm was voted one of the best speakers at Festival of Genomics in Boston by the crowd there. She only lost out to J. Craig Venter and George Church (and not by much!). What do all three have in common? They’re all at the very forefront of genomics. Heidi’s lab is responsible for an impressive list of ‘firsts’, and she is also heavily involved in building the processes and infrastructure to help make precision medicine a much more powerful reality. But where did her journey begin, and what keeps her motivated through a very hectic schedule?

FLG: Starting at the beginning, where did your interest in molecular biology and genetics come from?

HR: Well, my father was a high school biology teacher, so that might have had some influence on me. I remember going back to my, what was it, my 20 or 15 year high school reunion where we’d put what our careers would be, and I wrote genetic engineer. So I was pretty close. I just loved biology, and specifically genetics, when I was a kid. In college I majored in molecular biology and biochemistry. There wasn’t a genetics major at Middlebury, so that was the closest area. Then I worked in a research laboratory, which at the time seemed the only career option in science. I spent the summer in college doing laboratory research, really enjoyed it, and so decided to pursue further work in the lab. That led me to a PhD program, and I got my PhD in genetics.

FLG: What led you to setting up the Laboratory for Molecular Medicine at Partners HealthCare?

HR: In addition to loving genetics, more specifically I liked the clinical relevance of studying human disease. So when I came to Harvard for graduate school, I selected a Human Genetics laboratory to do my PhD in, and that landed me in Cynthia Morton’s Lab studying hereditary hearing loss. When it came time to get a post-doc, I loved the field of hearing loss, and I wanted to stay in it. Usually in a post-doc you try to branch out a little, so I decided to do a post-doc in a lab that was doing more neurophysiological approaches to studying hearing loss. So I went to David Corey’s Lab in the Neuroscience Department of Harvard to do my post-doc. But within a year or two, the opportunity arose to build this new center that at the time that was called the Harvard Partners Center for Genetics and Genomics. Cynthia, my PhD advisor, was a part of some of the planning for that center and suggested my name as someone who would be good to help build a new clinical lab that would be part of that center. It was sort of a perfect marriage of doing genetics, but also applying it to human disease. I agreed to take the position to build a new clinical lab, and that’s really where I started, you know, and that was 2002. So it’s now been, what, 13 years since I started building the clinical laboratory.

FLG: That came at a pretty exciting time in genetics. How have you seen the nature of the projects that you’ve been involved with change over the years?

HR: Well, we were one of the early labs to really use high-throughput Sanger sequencing in a clinical diagnostic setting, which seems a little silly today, but that’s where we were in 2002. We were the first clinical lab to launch chip-based sequencing, which again seems a little archaic at this point. We designed this laboratory to be positioned within a cutting edge research core facility environment supporting genetics and genomics research. We situated the lab smack in the same space as all these core facilities, which allowed us to translate those technologies very rapidly into clinical use. →
So we took the whole facility that had supported the human genome project through Raju Kucherlapati and just turned it over to applying it to clinical sequencing. We were able to scale Sanger sequencing, more so than any other clinical lab. And then later we were one of the early clinical labs to launch next-generation sequencing.

We were also the first lab to bring EGFR (epidermal growth factor receptor) testing for somatic cancer to determine the appropriate treatments for lung cancer. We launched that test within three months of the publications in Science and Nature on the discovery of EGFR mutations underlying lung cancer and rapidly launched the test in collaboration with the two pathology departments at MGH and Brigham & Women's Hospital/Dana-Farber Cancer Institute to get that test to market in three months' time. So we've really been at the cutting technology edge in terms of bringing new technologies and tests to market.

We're at a different time now. Everyone else has caught up. There's actually an incredibly competitive market for genetic and genomic sequencing out there. Everybody now is at roughly an even keel. Everyone has launched next-generation sequencing for both germline genetics and, frankly, most of somatic cancer testing has moved to next-generation sequencing as well. It's now competition based on pricing and services and billing, the third-party billing and, you know, all the sort of additional services. It's more about how fast can you do it, how cheap can you do it, and what are the extra services you're providing that makes it easy for the physicians. The academic labs used to be leading the charge but now fewer and fewer academic labs can compete at scale and more commercial labs have entered the market with heavy financial investment that enables rapid innovation. So now we've started to increasingly focus on translational genomic projects supporting NIH-funded implementation efforts like the MedSeq project, the BabySeq project, eMERGE, ClinGen, that are helping translate and implement genomics into the practice of medicine in an effective way.

FLG: We've been hearing a lot lately about the FDA's proposed guidance on LDTs. I get the impression that there is a lot of discontent around how they've outlined that process. There are certainly some who feel the FDA are hindering the application of new technologies. Do you have any views on that?

HR: It's a great question, and there's still a lot of uncertainty about what is to come. I wouldn't say there is a lot hindering it today because nothing has really been put into place yet, other than we've been a bit impacted on the research side. All of the NSIGHT newborn sequencing grants from NIH had to go through the FDA so our BabySeq project actually got hindered while we worked with the FDA to get the appropriate approvals to be able to do the study. But I actually haven't yet been impacted in my routine clinical service. It's more been the discussions that are happening to try to understand where the FDA is going with the regulation and proposals to increase it. They're taking a risk-based approach, which I think is a good general model to not impose regulation on in every single test, but to target those tests that put patients at higher risk. That risk may be based on the indication, it may be based on the context— is it direct to consumer or is it through a physician? And when you go direct to consumer that creates a higher level of risk to patients as it's happening outside of a routine clinical, patient-physician relationship.

Overall I am supportive of additional, I don't know if regulation is the right word, but ensuring high-quality testing is both available to patients and transparency in what those tests are and ensuring a minimal level of quality. At the same time, the question is, is it the
FDA that should be the ones regulating that or through CLIA and the CLIA accreditation processes, which is I think what most of us in clinical laboratory professions are advocating for.

FLG: You're very involved with ClinGen, which is playing quite a big role in helping make a lot of positive changes happen. How did you get involved with the project?

HR: I got involved in ClinGen, probably 4-5 years ago - before it was called ClinGen, back when a number of us lab directors were recognising the limitations in what we could interpret for patients. The sequencing technologies scaled. The amount of time each of our laboratories were spending interpreting variants increased and we were recognising the differences in interpretations that were happening across our laboratories due to inconsistency in standards for how we interpreted those variants as well as access to the actual data and evidence. The patients were being cared for differently depending on which lab, and who, interpreted the results. That recognition in the field as a clinical lab director offering genetic tests is what ultimately motivated me to say “How can we tackle this project?” Simultaneously, I became aware that some of these activities were being done already when I got involved on the molecular side in the cytogenetics community. There was an organisation called ISCA (Internal Standards for Cytogenomic Arrays), led by David Ledbetter and Christa Martin. It was really when the explosion of array CGH happened clinically, and that really was an incredible transition in the cytogenetics community going from karyotypes and FISH assays for targeted deletion analysis to all of a sudden using a full genome approach for copy number detection. And they recognised early on that the ability for laboratories to interpret all sorts of variation on cytogenomic arrays was a challenge and that data sharing was important. So they wrote a grant and got funding to share this data and to look at it jointly, developing better standards for what probes should be on a clinical array, et cetera. Later we ended up going in jointly on a grant, a U41 genomic resource grant, to extend the cytogenomics community's efforts, but then bring the same activity into the molecular community. After we submitted that grant, an RFA came out to support what then became called ClinGen. That was a specific request for applications to which a number of centers applied. So they held up our grant while they reviewed the other grants and they ultimately agreed to fund two grants from that RFA as well as our U41 grant and bring them all together. They asked us to come up with a joint plan for how it will all function as a cohesive project and then they funded all three grants. And that then became ClinGen as it exists today.

FLG: ClinVar is what we usually hear you speak about and is something you're very passionate about. My favorite statistic that I've heard you quote is – from the 11% or so variants with multiple submitters, about 17% of those are submitted with different interpretations. I think it's a really nice statistic, because it very neatly shows why ClinVar is so important. I guess there are two aspects of this. One is how did we get to this situation in the first place and how do we make it better?

HR: We've actually been doing subsequent studies that are helping answer those questions more concretely. One of those studies was presented as a poster by my postdoc, Steven Harrison at ASHG where we looked at four laboratories – my lab, the LMM, as well as GeneDx, Ambry and Chicago, who had collectively submitted over 32,000 variants to ClinVar. When we looked across those four labs, there was 87% concordance. We then focused on the 5% of variants that had differences that would have the most clinical impact to patients. That is one lab said it was either pathogenic or likely pathogenic, and another lab said it was either VUS, likely benign or benign. We've gone through 115 of those variants so far and we were able to resolve 71% of those.

We then asked the question “Why were they different to begin with?” Some of it was just simply a timing issue. Some of these variants had been interpreted over the span of 10 plus years or so, frankly the standards for interpreting variants were different 10 years ago. If I simply applied the rules I have today, I may immediately change that classification myself.

Some differences were due to delays in getting variants submitted to ClinVar ¬it's not a real-time interface to my database or anybody else's. We are submitting roughly once a year, so any variant in there could be as much as a year old. So some of the differences were just concordance between our own database in the submission process. Then the third was actual internal evidence. For example, if my labs does segregation analysis in a family, then I have actual real data that I have internally in my lab but no one else has access to. And simply by sharing that data we can agree upon a classification. Those are the circumstances where we could quickly resolve the interpretations as a group and that's what led to overall 71% of the variance being resolved.

On the other hand when we both had access to the same data and we both applied our current rules, some of the differences come down to how we weigh external data. So if a paper reports a functional assay and says this functional assay shows that the variant disrupts function, and one group looks at it and says, I trust that assay... and another group looks at it and says, I don't trust that assay...it's probably one of the biggest differences in variants that we aren't able to resolve today. And that is where we are working with expert panels to come up with better guidance on what types of assays are reliable predictors of pathogenicity.

The way molecular genetic testing used to work was that there were these niche laboratories that did testing in particular disease areas. Peter Byer's lab in the University of Washington are the experts in collagen disorders and a lab in Alabama is the expert in neurofibromatosis type 1, and so on. And so the people offering genetic testing were also the experts in the field. They knew the most about those disorders, those variants, those genes, everything, and how to make the best test that had the most comprehensive coverage of every gene and variant known to be relevant.

Now with moving to these large-scale platforms, really any lab doing molecular genetics can launch any test. However, there are two problems. One, knowing which genes really are relevant and which variants might not be picked up by the standard technologies of...
next generation sequencing make these platforms a little technically less superior. And two, they don't have the interpretive expertise when they don't understand the disease well, or the genes well. And so the coverage and the interpretations might be less effective and then the question comes, “Well, can the clinician fill in the gaps?” Unfortunately, clinicians are no more experts in those areas, necessarily. Sometimes they are but, usually not. That’s where we really need an authoritative resource to help guide this field, because I don't think the clinicians are going to be able to cover the gaps that the laboratory has.

Some laboratories really view the clinician as a partner. We call out our uncertain results, we discuss why they’re uncertain, what additional clinical testing might be useful to make them more certain. We offer free testing for affected family members to help encourage getting that information to figure out if a variant does or doesn’t segregate. And not every laboratory does that, or even when those samples come in, do they really apply that knowledge to their interpretation to refine it.

**FLG:** It sounds like you guys make a good effort to actually keep an open communication and, as you said, really work in partnership. Is that not typical?

**HR:** It varies. Most laboratories will have standard requisition forms that ask for clinical information upfront. However, the likelihood that we get that information is not always that high. But I will say, part of that is just the clinicians are busy, they don't have time. And if they don't think it’s necessary, they won't bother to do it. However, when we come up with results where it is clear that we can't effectively interpret without that information we reach out to the clinicians and it's incredibly likely that they are willing to take the time to give that information because they see the value. It does make for a little extra workflow on the post interpretation. So it does delay it, but I will say, in our minds, it's worth that extra time and the clinicians do feel its worth the extra time to work with us and give that information.

**FLG:** That's good to hear. Taking it back half a step to ClinVar again, I don't think there are too many people who would argue against the need for it. How are you encouraging people to submit that data and really get involved in and behind it?

**HR:** A variety of different ways. Some of the laboratories that were part of the original U41 grants, we are funding some of their staff to really build robust approaches to help support submission, but not every laboratory is funded. For the non-funded ones, they still do it because they just fundamentally believe that this is the right thing to do and are putting their own funds into it in a sort of collective way to realize that. Some labs are sitting and thinking “Am I losing my competitive edge by putting my knowledge out there?”
If you're the first lab to take that step, it's a little harder, but if you're the tenth lab to take it, it's like, "Well, everybody else is doing it and so, so should I." And in fact, having been the laboratory with the deepest knowledge in cardiomyopathy, I do not feel that sharing my data led to a loss in business from my lab. Right now, we're in more of the carrot approach, but this is going to turn to a stick approach. It's already getting that way. In the research space, there are journals that are requiring public submission in order to publish, so that's helping on the research side. On the clinical side, there are certainly hospitals and clinics that will only order tests from laboratories that share data. That's putting pressure on labs to share data. There are insurance companies that are starting to ask if you're sharing your data as a way to think about whether they will reimburse your test. So that's a big stick approach in the US. Conversations certainly have been happening on the accreditation end with organisations like CAP in the US on whether this will be a requirement of accreditation that laboratories must share their data. So these discussions are happening and, you know, some people might wait until they're required, others are getting out ahead of the game. Some labs are even using their efforts in data sharing as marketing, sort of like a green company. You know, maybe it costs them a little extra money, but they can market that and say, "You know, we're environmentally friendly, so you should work with us." And I think that marketing space is definitely helping some laboratories that are being the first adopters of this sort of data sharing approach. And then finally, and most importantly, we have found that it's actually improving the quality of the results that we can return to patients. If we can submit variant interpretations, compare them to other labs, identify the differences and work to resolve them, it improves the quality of patient care, and that in and of itself is an incredibly strong motivator.

**FLG:** That's fantastic. It sounds like some of the big barriers obviously have been around data sharing and creating not only the environment, but the impetus to make people actually want to share data and have it be a real incentive for them. What work needs to go into building a real-time clinical decision support system that can really handle that kind of data management?

**HR:** Actually, we just submitted a grant to NIH to create a health innovation platform. If every single clinical decision support rule requires deep interfaces into the electronic health record, that's just an incredible amount of work, you know, and that's going to stifle that process. If, on the other hand, we could create a basic platform for interfacing with the electronic health record, then you would more easily make it work the way the world of apps work. Anybody can create an app because you've got this common platform. It's very easy for people to create these apps, distribute them through a network, and install them and use them. That's not how it works in the EHR environment today. But if we created an environment where you really had flexibility in interfacing with that data, through standardizing interfaces to it, it would be much easier for people to innovate and create their best tool to support decision making in their clinic. We could get people to develop apps that could be broadly shared and installed in other EHR environments, test it out and constantly iterate on these things. Our grant is certainly about building that innovation platform to then allow subsequent apps to be inserted.

**FLG:** Cool! You've been involved and continue to be involved in a whole lot of different projects. As you look ahead, what's the stuff that's really getting you excited?

**HR:** A couple things. I certainly think this concept of a health innovation platform to really change how we think about healthcare today, and that we can make use in real-time of healthcare data. And as we move to accountable care environments, where we're being paid set fees per patient as opposed to per-service. It's going to be absolutely critical to understand outcomes and optimise expenditures and decision-making for patients that help improve their health. That whole environment is going to be critical on how we think about caring for patients.

So that's one piece that I think is really critical. The other is creating a much more effective interface between the clinical and the research environment. Recently, Daniel MacArthur and I applied to become a new Center for Mendelian Genomics and we anticipate receiving that grant in January along with three existing centers. And that is really in my mind about a better, effective interface between what I can do clinically today versus facilitating research when I can't answer a question for a patient. I think there needs to be a much more robust flow of cases that we can't solve today, particularly in genetic diseases, flowing into research where other methods and approaches as well as the aggregation of data can be brought together to actually solve those cases. That's sort of the next phase of what I'm working on where I've been doing clinic diagnostics for the past 12 years, and I see the limitation. We really need better data to understand penetrance of genetic variation and what the true risk is to these patients. So more emphasis on the clinical to research interface as well as innovative data sharing to amass lots of new information to solve the causes of disease and answer questions like what is a patient's true risk of disease given a genetic variant.

**FLG:** You always seemingly find ways to get out there and either, spread the word about ClinVar or educate a variety of different audiences at different levels. Looking back to our Festival earlier this year, I think you managed to prepare two presentations and chair a session as well. What keeps you motivated right now to actually maintain what has to be quite a demanding schedule and carry on being so active?

**HR:** The motivation is really that it's just an incredibly exciting time for genomics where we're really able to use genomics as a platform to shape the future of healthcare. We have the ability to create so much influence, how can I turn down the opportunity to be part of really pushing medicine in a different direction and thinking about it in different ways? So that's one thing that motivates me. I also find it incredibly rewarding to work in a team environment. And so a lot of these efforts in data sharing sort of force you to work with other people, and I find that just incredibly exciting to be able to share ideas to work together to come up with the best solutions, and that kind of interaction I find is highly motivating as well.
Around 25-30 million Americans are estimated to suffer from a rare disorder. That’s around 1 in 10 people. And for these patients the wait for a diagnosis, or for any kind of understanding about their condition, can be excruciating. The race to deliver meaningful genomic interpretation to patients is on, and leading the field is Alan Beggs, Ph.D, and his team from Boston Children’s Hospital with an initiative called the CLARITY Challenge.

“The CLARITY challenge was originally the brainchild of David Margulies, Isaac Kohane and myself,” explains Alan. “We organized that first Challenge at a time when the technology for generating genomic sequences was maturing, but the software for manipulating them was still being developed.”

CLARITY 1 (Children’s Leadership Award for the Reliable Interpretation and appropriate Transmission of Your genomic information) focussed on rare diseases. “In that challenge we chose three families, who had either been enrolled in research either in my own laboratory,” notes Alan, “or with the Manton Center for Orphan Disease Research, and who had conditions that were thought to be genetic, but we didn’t know yet what their mutational value was.” Two of the children had muscle-weakening disorders, and the third had unexplained heart defects that also affected several members of his family.

In all 23 teams from government labs, academic facilities and DNA diagnostic companies around the world explored the anonymised medical information, whole-genome and whole-exome sequences provided by the three families. The aim was to use these submissions to drive the creation of ‘best practice’ in genome analysis, interpretation and reporting.

“One of our observations was that a lot of people were using a lot of the same software,” comments Alan. “We thought that that challenge addressed the question of the informatics approaches primarily. A number of those teams did not include medical geneticists, and some of the entries consisted simply of a spreadsheet, and maybe one or two pages written by somebody who’s a mathematician or a computer scientist or an informatician.”

“We had been considering having a second challenge, and frankly we were planning to focus that on cancer genomics and genetics as we felt that would be something a little bit different than disease diagnosis.”

At that time, a chance contact with the patient community sent the second CLARITY Challenge in a completely different direction. Filmmaker and Clinical Director at the NeuroBehavioral Institute Katia Moritz contacted Isaac Kohane about her documentary project Undiagnosed: Medical Refugees, which explored the lives of patients living with undiagnosed genetic conditions. “The focus of that movie is the diagnostic odyssey many people have to go through and the impact that it has on them when they don’t receive a proper diagnosis,” explains Alan, “and when their medical caregivers essentially throw up their hands and say “I’m sorry, there’s no more we can do for you”.”

Katia herself developed an unknown syndrome following a routine endoscopy in 2010, and the need for greater awareness inspired her to create Undiagnosed to tell the stories of patients with mysterious, undiagnosed conditions. During the course of filming she worked with the National Institutes of Health Undiagnosed Disease Program, which lead to the contact with Kohane and the team at Boston Children’s. “Long story short, Katia Moritz and the movie producers were referred to the coordinating center for the NIH Undiagnosed Disease Program, and following some discussions they agreed that we would actually pattern our next CLARITY Challenge around these five families,” says Alan.

If the first CLARITY Challenge emphasised best practice in data interpretation, the aims for CLARITY Undiagnosed, as it became known, were to really develop the ways in which patients could interact with their information. Alan describes these diagnoses as “the toughest of the tough.”

“They’ve all got something that doesn’t fit cleanly into any known entities, and for which there are no genetic candidates ahead of time, but we felt, regardless of whether or not we were going to find smoking gun mutations, that the way the information that was found gets presented to them was really an area that needs a lot of development. That’s what we hoped this challenge would focus on.”

To make this happen, the 26 contestants involved in the Challenge were asked to develop their interpretation into a clinical report that could be used by a physician, and even the patients themselves, and that could be included in the medical record. Their reports...
CAROLINE YIU
Mother of Alex Yiu, CLARITY Challenge participant

“With the CLARITY Challenge the one thing that we were very excited about was that they had 26 different teams from around the world looking at this. And so it sure beats me knocking on 26 doors trying to present Alex’s case! We were aware of the genes that the Challenge contestants identified, but I just know that after 26 teams have looked and concurred, that we’re definitely moving ahead to confirming that these are disease-causing. And once we confirm that then maybe we can look for some better treatments and hopefully a cure ultimately. We’ve been very blessed that we’ve come across doctors, scientists and researchers that apart from being very good at their jobs, have very big hearts. They’ve gone well above their call of duty to help us find an answer for Alex.”

were put to a broad, independent judging panel including clinicians, diagnosticians, and specific clinical domain experts.

As the entries started to come in, Alan confesses that he felt a little twinge of disappointment that no clear diagnoses emerged for any of the patients. “There were no smoking gun mutations found,” he explains, “and honestly when I first looked at all the reports and when I looked at the data myself, you know my heart sank a little bit because I certainly hoped to be able to call families up and tell them that we found something meaningful for them.”

What the Challenge did do however was focus twenty plus pairs of eyes on these patients’ genomes, and while Alan’s “smoking gun” was not forthcoming, the contestants did manage to narrow down the search area. “In each family there are variants in genes that were identified by one or more groups that we think are worth following up,” he comments.

As with CLARITY 1, process and best practice remained at the heart of choosing the winner of CLARITY Undiagnosed. As Alan notes, “the winners weren’t chosen necessarily because they came up with the best candidate, but they were chosen because they might have had the best process for choosing those candidates, and they had the best way of explaining it.”

“Some of the better reports listed the genes that they examined and talked a little bit about what the sensitivity for detecting mutations in those genes might be. It was important for contestants to specify types of mutations that might not have been found or if particular genes were considered, to consider the coverage across that gene and make it known whether there were areas that were not adequately sequenced.”

Based on these criteria, with a report that “stood out head and shoulders above the rest”, the team from Nationwide Children’s Hospital lead by Dr Peter White was declared the winner. “One of the things that really set them apart was the fact that they provided two reports, both for the families,” says Alan. “They provided a clinical diagnostic laboratory report and they also provided a separate genetic counsellor’s letter for the family. That counsellor’s letter was very well written and in lay terms explained the results and the caveats, in a way that the judges felt was very good. Also for the clarity - no pun intended, sorry! - of their clinical report.”

“They also included an excel table which is not really part of the typical clinical workup but especially in the case where you’re returning results of unknown significance can be very helpful for families that want to have further testing pursued in other venues, particularly in research settings. They really covered the gamut from A to Z.”

Establishing the gold standard for best practice is the first goal for CLARITY. But having set the benchmark, how can Alan and the team at Boston Children’s Hospital spread the word and encourage other institutions to implement the standard set by Nationwide?

“We will try to do that by writing a paper,” explains Alan. “I hope that we can identify some of the common deficiencies that are seen, consider what some teams did that others didn’t, put it all together maybe we can come up with an ideal report.”

“I should say, you know,” he adds, “there is probably no one right answer though. I’m not certain that we’ll ever be able to come up with a one size fits all, and in a sense that was one of the nice things about the fact that the Nationwide group provided the technical report and then the separate letter to the patient.”

Looking to the future, what does Alan think CLARITY 3 might look like? “We get that question a lot,” he chuckles. “The answer is I’m trying not to!”

“I’m still trying to wrap my head around what we’re learning here. We all want to push this paper through, get it out and then think about the next Challenge. There are people coming up with suggestions and certainly cancer is still something that’s out there and that’s important. But we haven’t had any discussions yet about what or when to do it.”

CLARITY is a remarkable effort to bring together the individual efforts in genomic diagnostics to create something powerful and meaningful for patients whose test results have been years in coming. Ultimately, if the Boston Children’s Hospital team are able to provide a diagnosis for even a few of their patients, then in Alan’s own words, “it will all be worth it.”
DEVELOPING THE LARGE-SCALE DATA STORES OF THE FUTURE

Tim Wesselman, Founder & CEO, Onramp Bioinformatics

FED UP OF SPENDING ALL YOUR TIME TRYING TO BUILD INCREASINGLY ADVANCED INFRASTRUCTURE FOR YOUR RESEARCH? THE TEAM AT ONRAMP BIOINFORMATICS ARE MORE THAN HAPPY TO USE THEIR CONSIDERABLE EXPERTISE TO LET YOU GET BACK TO ACTUALLY USING YOUR DATA. CEO AND FOUNDER, TIM WESSELMAN EXPLAINS...

**FLG:** With sequencing technology developing the way it has over the past few years, genomics has become a very data centric field. How do the big data challenges within genomics compare to those in more mature fields?

**TW:** With social media, what we do, watch and buy has become the DNA of our online personas. Ironically, social media and eCommerce companies have deployed more advanced technology for the computation and storage of our online personas than what I’ve seen the medical industry deploy for our biological data. I recently read an interesting white paper, that compared the data demands of social media sites, to biological genomic data. It estimates that 2 billion genomes will be sequenced by 2025, and our biological DNA will be the biggest of all big data - producing 40 Exabytes of data. That’s 20 times more data than YouTube, and nearly 2500x the data Twitter has forecasted to generate at that same time.

Really, it’s all about convergence.

Today’s big data challenge in genomics can’t be solved with a single software application, just as it can’t be solved with hardware alone. Converging big data insights with genomic analysis and storage is the key to developing the competitive large-scale data stores of the future.

**FLG:** As an observer, it’s been fun to see so many new companies come into this space with their solutions. What would you say sets you guys apart from the crowd?

**TW:** We are currently the only ones that are bringing a converged big data platform to genomics analysis and storage. We enable the best of both worlds, highly scalable Software as a Service that is deployed on-site for our customers, so they get the performance and security of an onsite system that’s scalable, with the same economics of a cloud-based solution. Our customers want a solution that will not just last for the current grant cycle, but will grow and scale as their data expands dramatically and their needs evolve.

We built out a comprehensive suite of genomics analysis capabilities that provide powerful bioinformatic pipelines that are both easy to use and fully capable of customization. These analysis pipelines are auditable and highly repeatable.

Moreover, all customer data is stored at the customer site, in a highly-resilient and protected scalable storage system.

And this is just the beginning, because our platform also includes a full analytics engine powered by R, Hadoop and Spark. Through these technologies, we enable our customers to harness all their valuable genomic data, no matter where or how it is stored in their system. This is the key to enabling population scale insights.

**FLG:** You have an impressive list of partners already. Have you had any success stories from the use of your platform yet?

**TW:** We have been honoured to support research with the Medical University of South Carolina, the University of California at San Francisco and San Diego, City of Hope, San Diego State University, Phoenix Children’s Hospital as well as some pioneers in the Clinical Trial field.

Utilising the Genomics Research Platform, one of our customers has been able to process and generate more genomic data in one month than they had in the prior eight years. This has enabled them to catch up on research that was otherwise backlogged, and have awoken their institutions to the bioinformatics opportunities within their broader medical research and patient care.

**FLG:** Thank you for your time. Is there anything else you would like to mention to our readers?

**TW:** Specifically for readers who would like to speak to our team about a Genomics Research Platform solution, we gladly extend the opportunity to apply for a free trial program through our Front Line Genomics partnership link: www.onramp.bio/flg-free-trial.
TRUTH SEEKING AND HYPOTHESIS TESTING

Mene Pangalos, Executive Vice President, Innovative Medicines and Early Development, AstraZeneca

BIG PHARMA IS BIG BUSINESS. WITH SUCH HIGH LEVELS OF INVESTMENT, COMMERCIAL PRESSURES CAN CAUSE ONE TO LOSE SIGHT OF BASIC RESEARCH PRINCIPLES. WITH A FAILING PIPELINE, MENE PANGALOS WAS ONE OF THE KEY PEOPLE BEHIND ASTRAZENECA’S TRUTH SEEKING REVOLUTION.

“LEARNING FROM OUR HISTORY, BEING ABLE TO ARTICULATE WHAT WE’D LEARNED, AND BEING ABLE TO TRANSLATE THAT INTO HOW WE WERE GOING TO REFINE THE WAY WE WORK AND IMPROVE OUR OUTPUT WAS IMPORTANT.”

Since joining AstraZeneca in 2010, Mene has been an instrumental figure in transforming the company’s commitment to science. As well as driving collaborations with academic, NGO, and peer organisations, he has also been leading the truth seeking revolution that has been transforming the company’s R&D productivity. Ahead of his plenary presentation at Festival of Genomics London, we caught up with Mene to find out what it takes to put an organisation back on the right path. →
**FLG:** I understand you are a fellow graduate of the UCL Ph.D. programme. What attracted you to take that first step into a life of research?

**MP:** That’s right – I got my degree from Imperial and PhD from the Institute of Neurology, which is part of University College London. I’ve enjoyed science since my early school days and was always particularly interested in understanding how the brain works. I had no idea how a passion for science would translate into a career, given there were no scientists in my family, but when I achieved a first in biochemistry I thought it would be a shame not to continue my training – particularly since I enjoyed it so much.

I was accepted for a PhD at the Institute of Neurology, supervised by Professor David Bowen – he was one of the first scientists to discover the cholinergic defect in Alzheimer’s Disease – a breakthrough that led to one of the mainstay Alzheimer’s therapies of today, acetylcholinesterase inhibitors. I was also sponsored by Merck through my PhD which gave me an invaluable insight into the applied side of research alongside the basic academic research I was doing. And from there I’ve never looked back!

**FLG:** What prompted you to make the jump into industry?

**MP:** As I said, during my PhD I was sponsored by Merck. It was during this time I realised that what really interested me was translating research. The opportunity to take basic research and translate that understanding into the discovery of a medicine that could transform the lives of patients really excited me – it felt useful, meaningful and real.

I didn’t go straight into pharmaceutical research. My industrial supervisor from Merck, Dr Derek Middlemiss, advised me to do a post-doc in the US – to further my scientific knowledge, but also to experience a new culture and a new way of working. It was great advice which encouraged me to think about my development and career and take some risks. New York where I worked for a few years was wonderful and his advice to be adventurous and take risks has stayed with me over the years. I encourage individuals that work with me to think about their development and challenge them to take leaps that can accelerate their careers.

**FLG:** Your career has also taken you to the USA. Have you noticed any significant differences between the British and American research environments?

**MP:** Actually no, not so much. There’s clearly more biotech and pharma funding in the US, but in terms of the quality of the research in the UK and the US, I would say it’s high in both countries. One thing I have noticed – both in the UK and the US – is that the quality of research in our industry is really high and often as good as the research that we see in academia. It is a myth that pharmaceutical companies do not do great science. If you’re in a company that’s focused on high-quality drug discovery, high-quality understanding of disease pathophysiology, the quality of the research can be exceptional and compete with the very best academic laboratories.

**FLG:** On both sides of the Atlantic, we’re making concerted pushes towards precision medicine. Have these national projects changed your approach as drug developers, or are they in part a result of the increased importance of genomics in the drug discovery and development process?

**MP:** I don’t think it is national projects that are pushing us toward precision medicine. The explosion of genomic data and our increased understanding of disease enables us to better identify sub groups of patients within disease areas and thus tailor medicines specifically to those patients. National genomics efforts are worthwhile, though many are still in their infancy, but they will not doubt add to our understanding. I think what has really changed is the way that we think about drug discovery and the importance of understanding or defining the right patient – the most responsive patient to your therapeutic approach – and therefore the most likely to derive a treatment benefit.

Of course, improvements in next generation sequencing have resulted in an exponential increase in the volume of data being generated. What’s more, it’s going to continue to increase, which in turn will lead to an even greater ability to stratify patient populations, particularly for complex diseases where we have struggled to do this historically.

**FLG:** How do the economics change? We’re going from trying to produce drugs that everyone needs, to spending a lot of money to develop increasingly tailored therapies. Is the cost of drug discovery and development increasing as a result? Is there a possibility that the best treatments are going to be so individualised that they are also prohibitively expensive as with some orphan drugs?

**MP:** I think personalised drugs will be more expensive than traditional medicines because they are taken by a far fewer people. The economics will still have to make sense. I would rather pay for a medicine that works in 60, 70, 80 percent of the population and costs more than a cheaper drug that is ineffective in the majority of patients it intends to treat.

**FLG:** Outwardly there have been some very noticeable changes when we are competing with our competitors. That may be in terms of the way we interact, or the way in which we compete and lead in these areas, to drive our long term success.

**MP:** I’m not sure I completely agree with that. I think we’re a lot more open and transparent with academia and with partners where we have shared interests, but I wouldn’t say we’re more open when we are competing with our competitors. For example, I see target identification, target validation, new pathway identification as areas of major competitive advantage for us – and it’s important that we compete and lead in these areas, to drive our long term success.

I do want to be a great partner with the people that we choose to collaborate with. That may be pharma in some instances – our collaboration with GSK and Manchester University in inflammation is a great example of this. However, the majority of our research partnerships are with academic collaborators and biotech. We say we want to be at the cutting edge of science with you, generating data with you, not just giving you money and waiting for that data to come back. We’re working together, we’re making the discoveries together.
we're on the publications together as co-authors, we're sharing IP appropriately and everyone should benefit from the collaboration. If I was to look at the journey that AstraZeneca has been on over the past five years, we have shifted our culture to one that is much more open, much more collaborative, much more interested in understanding the basic science and working with the best academic groups to help push that science collaboratively.

There are also things that we are doing with industry, such as the recent compound exchange with Sanofi, which maybe 5-10 years ago we would never have thought of doing. We have looked at our compound sets, looked at what diversity we have and exchanged 200 hundred thousand compounds between our companies that we both feel will enrich our compound collections for screening. It's unusual, but we're one of the companies that have embraced this new of working.

**FLG:** It feels like the drug discovery and development paradigm has shifted significantly, now that we're moving past the 'blockbuster' era. Rather than taking a 'try it and see' approach or developing 'one size fits all' therapies, there seems to be much more focus on developing a more in-depth understanding of a disease and its pharmacogenomics properties earlier on in the process. How would you characterise the change in approach to discovery and development over the past few years?

**MP:** I think oncology research has been a key driver of this change – and cancer patients have seen the benefits of what we have been able to do. Lung cancer is an area we're very passionate about and exemplifies what's been happening in terms of a change in the landscape. Go back 20-30 years and lung cancer would have been defined by histopathology. Do you have small cell or non-small cell? Squamous or non-squamous? You would have taken your biopsy, taken it to a pathologist and they would have diagnosed you and received the devastating news that you have 6-12 months to live. Fast forward to the early 2000s and you've got the first oncogenes defined such as KRAS – the first genetic driver of lung cancer. Fast-forward another few years and you've got the second one in EGFR receptors, which yielded drugs like Iressa and Tarceva. Go forward to today and we've gone from having a couple of genes identified to more than 20 genes known to drive subsets of lung cancer. And what we've seen is that when we start to develop molecules that hit those specific subsets change the way we conduct clinical trials, enhance our patient selection, the efficacy relative to the risk and non-response is much much higher.

If you're on a drug like Iressa, you have EGFR driven disease but after 6-12 months of taking the drug your tumour may develop resistance to the drug. Two thirds of that resistance is driven by a very specific mutation called T790M.
By understanding that biology and that mutation we were able to develop a molecule that specifically targets the resistance mechanism. That molecule went into man two and half years ago, and it was approved as Tagrisso on Friday 13th November 2015. That's two and a half years from first in man to launch, which is the fastest-ever approval in the history of our company and our industry. This shows you the power of personalised medicine.

It's a breakthrough that we are applying in other disease areas such as asthma and COPD where the first drugs are getting approved now for patient populations stratified by how many inflammatory cells patients have in their blood or sputum. We're starting to stratify patients with lupus, Alzheimer's disease, patients with diabetes and cardiovascular disease. We are seeing it happen in more and more areas as we build a deeper understanding of the drivers of disease, even in complex non-monogenetic diseases. That's the excitement of what we see, and with the added benefit of next generation sequencing, where we can sequence not tens or hundreds of genomes but thousands and millions of genomes, the power of the data we can generate becomes even greater so we can hopefully start to see the impact of even subtle levels in genetic variation.

**FLG:** At AstraZeneca, you underwent a pretty extensive review of your pipeline which you published last year in Nature Reviews Drug Discovery. It was a remarkable insight into how a pipeline is managed, and a very honest appraisal of what was going wrong for the company at the time. The review is a powerful document for you guys, but what made you decide to make it public?

**MP:** Where we were as an organisation, our R&D was not well recognised. It had been perceived as destroying value rather than creating value – so from an external perspective, there were clearly things wrong with what we were doing and how we were making decisions. The output from the billions of dollars we were investing was not what we wanted to be as an organisation.

“The majority of our research partnerships are with academic collaborators and biotech. We say we want to be at the cutting edge of science with you, generating data with you, not just giving you money and waiting for that data to come back.”
I joined in 2010 to help transform the R&D organisation and the productivity of the company. Learning from our history, being able to articulate what we'd learned, and being able to translate that into how we were going to redefine the way we work and improve our output was important. It was important for us, but it was also important for people outside the company to see that we had recognised this. The fact that we understood some of the mistakes we'd made, and were going to redefine the way in which we work was important. It was important for the academic community to understand how we work, and important for people who might be interested in investing in us, and biotech companies, to understand our drivers going forward. The 5R strategy that we describe in the paper, it is all about driving truth seeking behaviour and having rigorous science driving our decision making. We were drawing a line in the sand and showing what things were going to be like going forward.

It obviously takes time to see the impact. We are starting to see this now with a number of regulatory approvals over the past couple of years as well as the transition of multiple projects into Phase III. Importantly, the value of the pipeline is far better recognised now as are the changes we've implemented and I think we are clearly creating value.

The other reason we decided to publish the paper, is because we think it's useful to the community as whole. Not just to tell our story, but also for scientists thinking of taking their project forward who maybe have an interest in starting a company. It shows what some of the caveats and pitfalls are, it is brutally honest about some of the lessons we've learned, and helps others to improve how they do their drug discovery and development.

That's the feedback we've received. People have found it a useful article because it goes through the things you need to be doing to make sure you have the quality and depth of thinking in your programme. Rather than just trying to get something through to the next milestone, you're trying to deliver a medicine that's differentiated, and that's what we're all ultimately trying to do.

**FLG:** It sounds like you've made people stop looking for reasons to progress candidates, but returned to a more familiar null hypothesis testing based assessment where you're looking for any possible reason to fail a candidate. That's something that a lot of people can identify with, whether their starting up their own lab, or biotech company, at some point they might realise that a change in culture becomes necessary. How do you go about making that kind of change?

**MP:** That's right. When you're doing your basic research training in academia, you're taught to be truth seeking and try to disprove your hypothesis. Once you start to become a biotech with one or two assets, trying to start your company, or running you project in a pharma company, it's very easy to think "I've got to make sure my project succeeds", and if it doesn't work out, it's viewed as a failure. What you change is that culture. You reward people for getting to the right answer, whether it's a progression or not. You've got to get used to failure, you've got to get used to thinking "I've tested my hypothesis and it was wrong, and that's ok", what's really bad is realising "I've tested my hypothesis and I don't know whether it's right or not, and I've just spend $20million doing this experiment". Obviously we want to succeed more than we fail, but it's actually failing well that's important, and rewarding that failure because we've done a good experiment.

The cultural shift was difficult, and has taken time – a good 3-4 years. What's changed is the output. People see that they don't get punished for stopping things. By being more rigorous in our scientific approach, we're actually seeing more things moving forward because we're getting better data. The real benefit we're starting to see now, is that we're getting drugs approved. That's hugely motivating and it's what we all came into this industry to do – deliver medicines that make a difference.

What's more, within our culture today we have a scientific underpinning to everything we do. We are not just asking our scientists to do great drug discovery, but do great science and publish it as well. When I first joined the company I asked our scientists to publish their science every year. Many said it's impossible, it's unreasonable, we don't have time. Once you get over that initial hump of everyone telling you that you can't do it, people realise that you can and that it's actually kind of fun, accelerates your career and your external reputation. It helps you feel good about what you're doing, give you regular peer review and critique and makes it a much easier place to attract and retain great scientists. That becomes the cultural shift.

**FLG:** In January you'll be stepping up on to the main stage at Festival of Genomics London. Your presentation is on ‘Harnessing the power of genomics and personalised healthcare’. That's a broad title. What will you be sharing with the audience?

**MP:** My talk is going to be about the importance of defining the pathway, the patient population, the unmet need, and then focusing your drug discovery programme on delivering to that. How do you take deep scientific understanding to pick the targets or pathways that you want to work on and how do you translate that to molecules you can test in the clinic and convert to important medicines.

The other thing I want to talk about, is the importance of collaboration. One of the reasons we're moving to Cambridge is to be in the middle of one of the best scientific hubs in the world, giving us access to some of the best science in the world. That's the other piece that I think is very important to what we do – getting involved in partnerships and collaborations and being a great partner.

**FLG:** Is there anything you're hoping to take from your time with us at the Festival?

**MP:** There are some cool talks there, I'm a scientist, and as a scientist I always want to learn something new and I think this is going to be a great opportunity to do just that.

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**References**

Just as physicists learn about new infinitesimal particles as they look more closely at the atom, deeper interrogations of the human genome have revealed far more complexity than ever anticipated. With each discovery — from population-specific structural polymorphisms to newly characterized regulatory elements — we learn a little more about how genomes encode function, and how our unique genetic code contributes to individual health and disease.

As DNA sequencing technologies become increasingly sophisticated, we can see the roughly 6 billion bases that comprise a diploid human genome more clearly than ever before, and appreciate that even our best “whole” human genomes are not as complete as we had hoped. For the past 15 years, the human reference genome maintained by the Genome Reference Consortium has provided an invaluable resource for the human genetics community. The current reference represents the most comprehensive and complete view of the human genome ever assembled. Yet, it is still plagued by gaps and systematically underrepresents the tremendous sequence diversity we now know to exist in global populations.

Common sequence polymorphisms such as structural variation, microsatellite repeats and highly repetitive elements (e.g., segmental duplications) are just a few of the functionally important areas underrepresented or completely missing. Sequence variation within many of these complex genomic features is known to cause common genetic diseases such as ALS, Huntington’s, Autism, Schizophrenia and Alzheimer’s, and has been linked to a wide range of autoimmune diseases. The medical significance of non-SNP variation at disease-causing loci even within the Northern European population further increases the urgency for discovering and better representing these regions in global populations, and sheds light on how these previously poorly characterized structural features of the human pan-genome contribute to heritable disease.

With a new generation of sensitive and highly accurate long read sequencing technologies, scientists are now on the path to resolving these difficult regions in a diverse set of human genomes, augmenting our knowledge of common structural variants that exist in global populations. In doing so, they are reporting completely novel findings, even about areas of the genome previously thought to be fully characterized.

**BUILDING A ‘PLATINUM-QUALITY’ HUMAN GENOME**

Between the original Human Genome Project and subsequent efforts to improve the quality of the data, the community has invested hundreds of millions...
CONCLUSION

of dollars into a high-quality, finished human genome reference. The assembly — currently build 38 (GRCh38) — still needs work, and that's why scientists around the world continue their push to achieve a near-perfect, or platinum-grade, genome.

A key advance has been the use of the hydatidiform mole, an unusual cell formed when sperm fertilizes an egg without a nucleus. The resulting DNA is human but contains only a single copy of the paternal genome, making it haploid and more straightforward to sequence and assemble. A group of scientists led by the Genome Institute at Washington University in St. Louis published a high-quality first draft assembly of this type of cell in late 2014 using BAC clones and 100x coverage of short-read data. Despite progress made using this method, the researchers reported that even this assembly had persistent errors in regions marked by structural variants and segmental duplication.

Other work with the same cell line from scientists at the University of Washington, University of Bari Aldo Moro, and University of Pittsburgh demonstrated the success of long-read sequence data in resolving complex genomic elements. With ~40-fold sequence coverage of Single Molecule, Real-Time (SMRT®) Sequencing, the team managed to close or shrink more than half of the 160 euchromatic gaps existing in the reference genome, many of them in GC-rich and repetitive stretches of DNA. The effort added more than a megabase of novel sequence (including putative regulatory sequences and novel exons) to the reference. This was reported as “one of the most comprehensive catalogs of structural variation” in a human genome. Many of the 26,079 structural variants they found were novel, including 85 percent of the copy number variants, 92 percent of insertions, and 69 percent of deletions. “Our results suggest a greater complexity of the human genome in the form of variation of longer and more complex repetitive DNA that can now be largely resolved with the application of this longer-read sequencing technology,” the scientists concluded.

The highly contiguous assemblies from these efforts were recently published and made publicly available through the GRC and NCBI. One of the studies reported near-complete de novo assemblies of individual chromosome arms (i.e., chromosome 6). The highly contiguous chromosome 6 sequence in CHM1 resolves many of the remaining annotated gaps, and will contribute to continued polishing of the human genome as the community moves closer toward a platinum-quality reference.

Generating New Reference Genomes for Global Populations

Many scientists also realize a need to generate reference-quality assemblies for additional human genomes. Population-specific reference genomes, for example, are beneficial for better representing the full size-range of genetic variation unique to a non-European population, providing additional knowledge of genome variation common to a population, such as insertion sequence, that may not be adequately represented in the current GRC build. Those portions of the genome unique to an ancestry-specific population then become accessible for follow-up genetic studies. This includes mapping of short-read data for genotype calling and for designing targeted genetic assays, such as PCR primer design. Population-specific references also provide a better match for genetic association studies conducted in a local population, and can increase the discovery of novel genetic polymorphisms.

Professor Jeong-Sun Seo, from Seoul National University and Korean R&D and service company Macrogen, recently used long-read sequence data, optical mapping, and BAC sequencing to produce a reference-quality Korean human genome. The assembly is more representative of genetic variation seen in Asian populations than the GRC assembly and has already enabled scientists to detect structural variants that may explain diseases more prevalent among Asian people, according to Professor Seo.

Separately, Craig Venter and his team at Human Longevity have announced plans to produce 30 reference-quality genomes with considerable ethno-geographic diversity. These assemblies will serve as the foundation for a larger effort to sequence and interpret 1 million human genomes in the coming years.

Two recent publications report assembling new and existing sequence data to produce higher-quality genomes more quickly. A team of scientists from the University of Maryland and the National Biodefense Analysis and Countermeasures Center performed an assembly of long-read sequence data as a test for their new assembly algorithm. The results, achieved much faster than could be done with other methods, yielded extremely long contigs and addressed many existing gaps in the human reference genome. The challenging MHC region, for instance, assembled almost completely into two contigs, compared to more than 60 contigs in an assembly generated from short-read data.

In another paper, researchers from the Icahn School of Medicine at Mount Sinai and other institutes assembled a diploid human genome, the well-studied NA12878, with long-read sequence data and genome maps, producing an assembly far more contiguous than is possible with other technologies. According to the paper, the work “represents the most contiguous clone-free genome assembly ever made, and is comparable to, or better than, other human assemblies employing mixtures of fosmid or BAC libraries.” This same group is now working on an Ashkenazim Jewish reference genome, with the goal of further resolving genomic features specific to this community and to support improved clinical testing and treatment of Ashkenazim ancestry-specific genetic disease.

Striving for Perfection

At the AGBT 2015 conference, the Max-Planck Institute’s Gene Myers — highly regarded throughout the bioinformatics field for his development of leading assembly and alignment tools during the Human Genome Project — commented that with long-read data and random error modes, it is now mathematically possible to achieve a near-perfect assembly of the human genome. That’s welcome news to the community of scientists constantly pushing to produce a complete, gap-free, error-free human reference genome.

As technologies improve even further, we should expect an explosion in the number of reference-grade human genomes available and consider the significant impact that will have toward empowering human genetics research. Ultimately, it will also open the door for delivery of customized healthcare based on the most comprehensive view of an individual’s genome. Today’s efforts to produce high-quality human assemblies will pay dividends in the years to come.

Luke Hickey

Luke Hickey, Senior Director of Human Biomedical Sequencing, Pacific Biosciences

Luke Hickey is Senior Director of Human Biomedical Sequencing at Pacific Biosciences. He has 16 years of experience in the genome technology industry, holding various R&D, Marketing and Commercial roles at Pacific Biosciences, Affymetrix, Ingenuity Systems, Incyte Genomics and UC San Diego.
COLLABORATIONS AND ENABLING PRECISION MEDICINE

Mark Stevenson, Executive Vice President and President of Life Science Solutions, Thermo Fisher Scientific

AS ONE OF THE KEY SERVICE PROVIDERS AND SUPPLIERS FOR THE LIFE SCIENCE COMMUNITY, THERE’S NOT A LOT THAT THERMO FISHER SCIENTIFIC AREN’T INVOLVED WITH. SO WHO BETTER TO TALK PRECISION MEDICINE WITH THAN THE MAN LEADING THE WAY ON THEIR LIFE SCIENCE SOLUTIONS?

If you work in a lab, chances are there’s a Thermo Fisher Scientific catalogue near you. There’s also a very high chance that one or more of their products are crucial in helping you do what you do. As Executive Vice President, and President of Life Science Solutions, there isn’t much that Mark Stevenson isn’t involved with at some level. Given the scope of projects that Thermo Fisher Scientific are involved in, he gave us an interesting perspective on how precision medicine is becoming a reality.

FLG: When we started up Front Line Genomics, one of the first things we had to do was try and build partnerships with some of the major organisations serving the industry. Thermo Fisher Scientific were right up there on our list, as you guys have been such an important name in life sciences research, let alone genetics and genomics for so long. What are some of the research projects you’re most proud to have had Thermo Fisher support throughout the years?

MS: Well, I’ll give you three examples of recent projects that we feel particularly proud of in the genomics area. The first one is a collaboration we’ve had with the Saudi Human Genome project. We worked with them because there is a really strong genetic basis of disease in the Kingdom. Together we developed and validated, in a very comprehensive effort, disease-causing genes of the population of the country and the Arab peoples. What we developed was 13 gene panels that really cover all the Mendelian diseases that we knew about in the kingdom. The authors of the initial research published earlier this year. They found that there’s a particular clinical significant advantage of doing broader exome sequencing due to lower cost. So that’s the first one that I would really highlight where we really felt we could drive into the future personalized medicine in the kingdom as an example of what genome sequencing could do.

The second one I’d highlight is one here in the US. We focused on cancer, and really with the National Cancer Institute (NCI) a program they called MATCH. We developed the use of our NGS technology and the whole system through a clinical trial where we standardised and validated the assay for all patients. The program was done in combination with the USAFDA. And what it is is a 3,000-some-pool clinical trial where we’ve got multiple clinical laboratories sequencing tumor samples. And what’s really unique about it, is it’s really a multiple-arm study where we’ve got 20-different treatment arms and including agents from multiple different pharmaceutical companies. It’s one of the things that President Obama has talked about in precision medicine and one of the arms of that is getting a collaboration, in this case between the National Cancer Institute, a hospital, a company like ourselves and with pharmaceutical companies, so that you can make treatment decisions based on the genetic profile of a tumor. And so, again, it’s a demonstrated program.

And then the final one I’d mention is the collaboration we’ve done with the Icahn Institute of Mount Sinai. The team worked together to develop a large targeted gene panel, not only for oncology, but other diseases. The Icahn Institute called this the Resilience Project, and what they’re really doing is identifying and better understanding...
genes and other factors that may protect certain individuals from developing rare catastrophic diseases.

I think all of those are great examples of what we can all do together. I'm a huge believer that if we can demonstrate the future now in these individual examples, then others will see them and adopt them, and we can collaborate and develop that in future to make it a reality.

**FLG:** There are a lot of national sequencing projects running around the world at the moment. From your point of view, what kind of impact do you think that they're actually going?

**MS:** Well, I think at the research level, the volume of discovery of new genes is immense and it unravels the complexity that we know exists in human biology. I think what we're finding at the clinical level, is that to get that adoption it really needs to fit into the clinical infrastructure to make it actionable. So the physician doesn't want to be deluged with a wide range of information. We really need to make it fit so that at the time, and this is what we've got in the NCI MATCH program- they're trying to decide the therapy for a patient with tumor. That's the decision they're trying to make, so can we sequence the genes that we know are associated or have a drug associated with them? Then they have a decision guiding and aiding tool as they make that diagnosis. So I think those are the two aspects and they're really on two different tracks at the moment.

**FLG:** What's your assessment on where we're really at with precision medicine, today?

**MS:** Well, I think we're just at the early stages, but there are some good examples where we are already using these tools to aid in the decision-making. I mean, one of the examples we've highlighted often is in pharmacogenomics. We know today 300 billion is spent in pharmaceuticals every year, yet it ranges between 20% to 75% do not respond correctly to that medication. Yet we see a good adoption now of small testing of SNP panels that allow people to do not respond correctly to that medication. Yet we see a good adoption now of small testing of SNP panels that allow people to

**FLG:** What would you describe precision medicine? What does it really mean to you?

**MS:** Well, what we're trying to do is target more precisely and individualise the meds more specifically to the disease and to the patient. The technology is helping us do that together with an understanding of the biology of the disease. I think it is all encompassing, because it changes the way we think about drug development and targeting, that changes the way we do clinical trials and then it changes the way we take the patient, diagnose them and choose the right therapy to be successful. So all of those things I think are encompassed now in the term of being more precise and how we're targeting our medicines.

**FLG:** For me, one of the exciting things is that, as the scope of what's possible through various technological developments increases, we're actually able to ask increasingly sophisticated questions. How do you see the trend towards incorporating multi-omic data to give a much more detailed understanding of a biological system progressing?

**MS:** Yeah, it's very clear that genomics and expression gives us one part of the story, but also at the functional level we need to look at the protein level. And so I think a multi-omic approach is going to be increasingly important to providing diagnostics. It is incredibly important. The Lancet Oncology published a collaboration that we did, together with the Karolinska Institute, looking at a prostate cancer test to see if we could replace the widely used but also maligned PSA current testing. And what you'll see in Lancet is an analysis on a combination of six protein markers and more than 200 genetic markers from a study of we did of 60,000 men aged 50 to 69 over a two-year period, 2012 to 2014. What we've shown is this new combination of protein and genetic markers really reduced the number of unnecessary biopsies. And often what's happened is you've taken the tissue sample from them, they turned out to be cancer-free and that's been about 40%. So what the new test found is that we get aggressive cancers in men with low PSA values that are currently going undetected. It's a very exciting publication and an example of how you can combine protein and genetic markers together.

**FLG:** Well, this is one of the really exciting things. Right now we're looking at genetic information and certainly pulling in stuff at the protein level, as soon as you start factoring that in with health records and real world data, you start to get into a very different kind of world, which brings about its own kind of problems. How far away are we from really being able to really make good use of all of this data?

**MS:** I think we're still quite away from being able to harness that. I mean a lot of the issue is that the data sources are in different formats and it's rare to get a health system that is contained enough to bring all that data together. Often, those are the collaborations we've been looking at where we can be part of that ecosystem and collaborate with that. But we're not yet at a point where the various data sources are easily aggregated together and can be used in a readily actionable way. So it's a large opportunity that exists out there.

**FLG:** What are the big challenges out there that still need to be overcome?

**MS:** Well, the barrier is to use the data that's been generated in an actionable way to change clinical outcomes. Our approach has been two ways on this. One, we try to take the large data sets that are being generated and produce them into actionable targeted information, which is what we've done in our NGS system. The second thing we've done is enable groups to host data sets in a common format. So we've just made available throughout Thermo Fisher cloud not only genomic, but proteomic data sets can be stored in the same file and also shared across the world.
in collaborations, which is increasingly important. We’ve seen that as well in some of the health outbreaks and public health things recently in SARS and before that in Ebola where the healthcare systems want to share data and the use of the cloud is a tremendous way to share those data sets in a simple way.

**FLG:** You mentioned companion diagnostics a little bit earlier. What is your read on the current state of companion diagnostics and how you see it changing as technology keeps developing?

**MS:** Well, most of the companion diagnostics approved today are still one-drug one-gene or one-protein tests. Our vision of the future is a multi-set genomic, more standardised panel and protocol. And what we’ve been doing is working with several major pharmaceutical companies to develop that standardised protocol to have their drugs on that system, and then submit that to the FDA and other regulatory bodies so that we can bring that to the larger and distributed clinical cancer community. So that’s really the change we see away from this one-biomarker, one-test approach that makes approval of drugs costly and time-consuming, to this NGS-based more standardised panel that several of the major pharmaceutical companies are now endorsing with us.

**FLG:** How would that regulatory process look like for something like that?

**MS:** So it would be a joint submission to the regulatory authorities with the validated biomarkers on that panel. The panel may have other markers on it. The drug would then be approved in a clinical trial and also in the regulatory way with that panel, with that system for that drug. What’s important is then when you’re testing in the pathology lab that pathologists would have a standard panel that could then select amongst different drugs on the market.

**FLG:** How does the regulatory framework need to adapt to encompass that kind of testing capability?

**MS:** Well, I would say the regulatory bodies have been very forward-looking in adopting NGS and thinking about new pathways. And what it needs to adopt too is how to analytically validate those representative markers on the panel and find an efficient way to do that. And if we can do that, then it’s much easier that those are available for labs to run and the current LDT framework can also evolve in using these available and validated panels rather than having to allow them to homebrew and develop their own panel set. So I think the regulatory framework is evolving and moving with it. There’s always going to be some more rare diseases and more rare gene sets that are going to need a different pathway to come through. But I think if we can validate the main system, which we’ve certainly done with NGS, and receive FDA approval on it, we will continue to expand the applications for it. I think that pathway is becoming clearer.

**FLG:** Well, speaking on NGS, Life Technologies obviously had a very important role to play in the early development of the sequencing market. What’s your read of the market as it stands today, and looking at Illumina’s position, what do you see as the big opportunities for other platforms to really differentiate and distinguish themselves?

**MS:** Well, the large opportunity we’ve focused on is targeted panels. In real clinical settings they have limited samples, because they want to do other tests or the biopsy doesn’t give them material, but still need rapid turnaround in a decentralised clinical lab. That’s been our focus and the opportunity. And we think it’s quite a sizable market. We’ve focused our NGS technology, the Ion Torrent technology, which has a good fit in that application and we’ve seen good adoption in that market. So that’s been our focus and will continue to be. As we look at other clinical applications, we’ve also recently expanded that NGS testing to transplant diagnostics, which also requires a fast turnaround as they’re matching patients to the donors. So that’s also an application we’ve been developing with our transplant diagnostics team.

**FLG:** We’ve had quite a broad ranging conversation on the nature of precision medicine and some of the key technologies and applications driving that change. How do you see the field looking developing over the next five years?

**MS:** I think over the next five years we’ll continue to see the trend of just more discovery of the pathways around disease and large investment in that discovery, and then continued rapid adoption in the clinical setting, where we’re proving clinical utility. I think both of those things are going to continue to happen and will happen somewhat in parallel as we take the information that’s discovered and we apply that to real clinical applications.

**FLG:** Looking ahead a little further, what would you expect it to look like in 10 years’ time and how would you like it to look in 10 years’ time?

**MS:** Well, I think in 10 years’ time we will certainly see the real-time use of genomics in clinical practice. I think that adoption will happen. I think the economics in clinical utility are compelling. The only question is how many diseases have we applied that to and that will probably be limited by the therapies available to intervene.

Now, what I hope will happen, is what’s happening now in oncology with the targeted treatment can also move out into other therapy areas. We don’t understand enough yet in some of the immune-related diseases, some of them, called aging diseases, some of the cardiologic diseases. As we expand out our understanding at a molecular level, we can develop more therapies that that will precisely target. So that’s what I would hope beyond what we’re doing today in some of the cancer and some of the obvious genetic diseases they inherited, diseases like we did in Saudi and other places that have that genetic burden.

**FLG:** I think given the scope of precision medicine, that progress is going to take a lot of different stakeholders to try to come together
and work in collaboration and certainly coordinate efforts very stringently. In your opinion, what are the key events or key things that need to happen to actually make that 10-year vision a reality?

**MS:** Upfront, it's the collaboration with the major developers of therapies, right? As a community between ourselves we, the technology providers and the pharmaceutical companies, need to be able to call the academic groups in that are discovering and understanding pathways. So that kind of collaboration has already started. I think it requires continued funding into that as government priorities from NIH, which the pharmaceutical companies are required to seize that as an opportunity that exists.

Then downstream, there's a change in how we do clinical trials towards smaller patient cohorts, but more effective trials. And then in the clinical setting, the adoption of the data that is being provided and then presented to a decision-making group that can be actionable, we need to format that in a way that can be actionable. Then we need to prove all of that to the regulators and reimbursement communities, providing the necessary pathways for the new treatments and medicine.

**FLG:** What would you say the next kind of big technology jump is going to be that's going to open things out again? I think the last really big one was NGS in the way that it just made things a lot more accessible and easier to do.

**MS:** Yeah. I think we're in a stage where although it's easier to do, we're still a long way from NGS being simple and straightforward. I mean if I compare to where we are in other technologies, we've got quite a way to actually make it a straightforward tool in interpretation. So I think part of our journey is taking that technology and making it more straightforward. So I think that's one of the next steps we are really focused on.

**FLG:** We've not really talked about your journey and how you got to where you are yet. If I remember correctly, you were formally a chemist way back at the start, right? What first got you involved and interested in science to pursue as a potential career?

**MS:** Well, I was always fascinated by science and medicine. I studied chemistry somewhat because I wanted to understand more at a fundamental level what was going on. I got more interested in the commercial side as it was fascinating to go out and visit customers around the world and engage in their science directly. So that journey led me from where I was born and grew up in the UK to a couple of years living in Sweden, then Japan, before moving to the US back in 2004.

**FLG:** Are there any places in particular that you enjoy living in more than others?

**MS:** Well, they all have their advantages, right? It's hard to argue with the climate here in California, but I certainly miss English football living here in California.

**FLG:** I've got to ask the question, who do you support?

**MS:** I'm a Manchester United supporter. We're doing better this season.

**FLG:** Good stuff! Looking specifically at your career within Thermo Fisher Scientific, it looks like an interesting journey that you've had in terms of always getting brought into increasingly larger organisational structures through a variety of mergers, from Applied Biosystems through to Life Technologies and now being where you are, pretty high up in the Thermo Fisher Scientific hierarchy.

**MS:** Well, when I started in Applied Biosystems, it was an exciting time back in 2008, we were just enabling sequencing of the first genome, and I've always looked at sort of the exciting things going on in wherever I am in the roles. When I moved to the US, my role was to try and develop the forensics business and a some other applications which we've done successfully over the last 10 years. As the company gets bigger and my roles have gotten bigger, I still have huge passion for what we can do with all of these different groups of customers. We've been fortunate in that we have more resources and technologies to apply to a lot of this. Now at Thermo Fisher, it's not only a broad range of genomic tools, but also we help our biotech customers scale up in my group. We have a broad range of molecular biology and core basic science tools, yet this industry remains very nimble, very fast moving, and I try to continue to keep that culture and intensity within our team even now we're part of a larger company. That's been the enjoyment of the journey.

**FLG:** When the time comes to really look back over your career, is there one thing in particular that you really would like to know that you've accomplished?

**MS:** The accomplishment for me is taking what we understand of the biology and making it part of a routine. The example share with people is how I think about forensics now- 10 years on it's routine for a jury to ask for DNA evidence taken when we're looking at whether we convict or exonerate somebody. And to me, I would like to look back the same when we look at clinical medicine and practice- someone goes and they're diagnosed with cancer, the first question should be routine is, "Well, what does the genetic profile say?" And that's not routine today. It is routine for everyone who watches CSI and forensics, but it's not a routine. So I would certainly like to look back and say we've made it a routine tool.
IT’S ALIVE! UNFORTUNATELY...
A WELL TIMED FILM ABOUT SCIENTIFIC INNOVATION CHALLENGING WHAT WE ACCEPT AS NATURAL. VICTOR FRANKENSTEIN PROMISES SO MUCH BUT DELIVERS IN ALL THE WRONG WAYS.

Victor Frankenstein has come out at the perfect time. As the science community, the general media, and the public are all discussing the merits and dangers of genome editing, what better way to frame the argument than with a classic tale of a misunderstood genius pushing the boundaries of what is scientifically acceptable? And the film truly delivers on producing an interesting argument in favour of developing technologies that challenge the natural order of things. As Igor cautions Frankenstein on his plan to reverse death, the latter reminds him that history is littered with technological advances that seemed dangerously unnatural at the time. He then goes on to say how much good could come from his revolutionary work, and that it is therefore his duty to pursue it. They could very easily have been talking about CRISPR.

In the case of genome editing, we are pushing the boundary of what we’re comfortable with as human beings. While we’re not creating life (although I’m sure that will come up as the field of synthetic biology develops), we are designing life to a certain extent. If we potentially have the tools to help ensure people lead healthier lives, rather than suffer through a disease, is it our moral obligation to pursue it? Interesting questions, that are extraordinarily relevant today. It’s great to see films challenge their audience to think about these things.

If you’ve made it this far into the review, you might be asking yourself “Hang on a second, I’ve read nothing but terrible reviews of this movie...” That’s right. All that I’ve described so far takes place within the span of about 20 seconds. The rest of the film is bad. Really bad. There’s too much wrong with it to fit into one review.

VERDICT: BAD
Bad writing is at the heart of this terrible film. It could, and should, have taken viewers on an interesting journey through moral obligation as it relates to scientific endeavour.

PROS
- A nice exchange as Frankenstein explains the rationale behind his work to Igor
- McAvoy delivers angst very well
- There’s a science montage in true Team America style

CONS
- Extremely underdeveloped characters
- Daniel Radcliffe’s hair
- Everything else in the movie

The film is flawed from the start with weak writing, in particular the inclusion of Inspector Turpin (Andrew Scott) to introduce some ham-fisted religion Vs science into the mix. Although James McAvoy has plenty of opportunities to shine as a tortured, and self-destructing mad scientist, his role offers no opportunity for subtlety. I can only assume Director, Paul McGuigan, kept shouting at him between takes to ‘go more intense’. To his credit, McAvoy does a great job. The problem is that he isn’t afforded much opportunity to flesh out his character. By contrast, Daniel Radcliffe probably has the more ranged role. Unfortunately, his hair is incredibly distracting. This is one of his performances to file away under the ‘I still see him as Harry Potter’.

If you’re looking for something to watch over the holidays, it’s best to steer clear of this one. Save your pennies and go watch Star Wars instead.

RATING
2
DEMAND PRECISION
BECAUSE FINDING THE RIGHT ANSWER IS EVERYTHING

Delivering on the promise of precision medicine takes getting results that bring clarity to the complex. We are dedicated to developing solutions for oncology, human and reproductive genetics and life sciences with precision that outperforms -- so you find answers that make a difference.
LEAD NATIONAL-SCALE GENOMIC PROJECTS

We are scientists, engineers, communicators, and data lovers. We are musicians, homebrewers, yogis, cyclists, and chess players.

Our team is passionate about how genomics and technology can impact and improve human health. And, as part of an innovative startup building the most advanced cloud computing platform for biomedical data analysis - that impact is huge.

At Seven Bridges, turn your ideas, research, and software into tools used by researchers around the world.

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