THE GENOMICS ERA HAS BEGUN

BUT WITH ADVANCES IN TECHNOLOGY AND ITS USE, ARE WE DOING ENOUGH TO ADDRESS HEALTHCARE INTEGRATION?

SOLVING THE INCIDENTAL FINDINGS DEBATE
Dr Anna Middleton talks us through her ground-breaking research on patient attitudes.

LONG READ SEQUENCING – THE STORY OF THE YEAR
Why is there so much excitement around long reads. Are they taking us further than short reads can?

PIONEERING NGS
We speak with Nick McCooke, the man who built and led the pioneering team behind NGS technology.
De novo Sequencing
Whole Genome Resequencing
Exome & Target Region Sequencing
Optical Mapping

RNA-Seq (Transcriptome)
RNA-Seq (Quantification)
Digital Gene Expression Profiling (DGE)
Non-coding RNA Sequencing
Degradome Sequencing

Proteome Profiling
Gel Band / Gel Spot for Protein Identification
Quantitative Proteomics (iTRAQ, label-free)
Targeted Proteomics (MRM)
Phosphoproteome Identification
Targeted Small Molecule Quantification

Whole Genome Bisulfite Sequencing (WGBS)
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ChIP Sequencing (ChIP-Seq)
Reduced Representation Bisulfite Sequencing (RRBS)

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The past few months have been a whirlwind of activity on all fronts. Ebola was still making the headlines for the wrong reasons; cancer genome cloud pilots were announced; ASHG 2014 took place in San Diego; Genomic England continued to take genomics to the masses, and Front Line Genomics launched!

September and October are always busy months, as summer holidays fade away into fond memories. For us here at FLG, September was the start of an exciting journey. After moving in to the offices it was straight to work. Our CEO Richard, and our Commercial Director Freddy, went straight into preparing for ASHG; our Head of Production, Aoife, was straight on to building Front Line Genomics Boston (takes place in June, and is going to be amazing), and I got down to figuring out the themes the magazine should concentrate on.

Without a doubt, ‘Data’ was the biggest challenge that kept coming up. Data is an enormous topic to look at, and something that could fill up several monthly magazines, let alone one issue of a bi-monthly.

For this issue we are looking at some of the new advances in sequencing technology that are set to take genomics in exciting new directions. Then we have some very interesting interviews that show some of the challenges and opportunities that genomic data will open up for us.

I do have a confession to make. In my own time spent ‘at the bench’ I had a set view of bioinformatics and bioinformaticians. I’m sure it probably wasn’t too dissimilar to the stereotype you might be thinking of now. Having come through the other end of this issue, I have nothing but respect and admiration for these people. I was fortunate to work with Saccharomyces in my research. Apart from the lab smelling like a bakery every day, the real benefit was the Saccharomyces Genome Database. Looking back on things, all I really used it for was designing PCR primers. I can’t help but feel that befriending a bioinformatician may have helped me do even more.

We’ve also noticed that the public are becoming more aware of genomics, as it seeps into popular media. This is a great sign of success for the field, but does now present a new challenge. Addressing misconceptions, and managing expectations held by the public is going to be an important part of what we all do.

I hope you enjoy this issue of Front Line Genomics Magazine. I’ve met some very inspirational and helpful people along the way. We’re still a work in progress, and always keen to hear from you. If you have any feedback or an idea you’d like to share, get in touch!
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Managing Editor, Carl Smith, reflects on the first few months of FLG and discovers a new found admiration for bioinformaticians

4 MAKING THE MAGAZINE
Find out who helped put the magazine together and who contributed to this issue.

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We look back on ASHG 2014, the 100,000 Genomes Project and Ebola.

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The Man Who Commercialised NGS – We interview Nick McCooke, who reflects on his time at the helm of Solexa and developing NGS technology.
**FIRESTARTER**

Is The Delivery Of Genomic Medicine About To Be Overtaken By Patient Demand? – Is the field of medicine ready for the use of genomics en masse, or do we need a road map to take us there?

**INTERVIEW**

Curing The Un-Curable – Despite being a notoriously difficult disease to treat, Michael Vellard has recently had his Morquio’s Syndrome drug approved. He shares his fascinating story with us and discusses the ethical dilemma of rare disease research.

**EVENTS**

A preview of what to expect at Front Line Genomics Boston next June

**REVIEW**

The Amazing Spider-Man 2 – What does The Amazing Spider-Man 2 mean for the public’s perception of genomics?

**COMMENT**

Long Reads – The Story Of The Year – What led us to short reads in the first place, and what does the future of long reads hold?

**INTERVIEW**

NGS Is Here To Stay, Now How Do We Use It? – David Smith talks about the changes that genomics will bring about and what we need to do to prepare for them.

**FEATURE**

Into The Heart Of The Storm – The current shortage in talent is a result of the success of bioinformatics. Read on and find out why a solution is on its way.

**INTERVIEW**

Letting The People Decide – Anna Middleton is about to publish the world’s first empirical data on patient attitudes towards incidental findings. Here she shares some of the main findings and what they might mean for healthcare.
The making of the 1st issue took a collaborative effort from a lot of different people. Carl Smith, Aoife Gaffney, and Laura Rae have been calling, e-mailing, tweeting and variously reaching out to as many people as possible to find the themes and stories that are defining the field of genomics.

On the design side, Daniel Wentzell has taken an abstract concept to create the fantastic look of the magazine. To get away from the traditionally stale B2B trade journal aesthetics, Daniel took his inspiration from an extensive investigation of consumer magazines to come up with something vibrant and eye catching.

Researching and developing the magazine requires the input of people active in the field. Four people have been absolutely instrumental for this issue, by contributing specific domain knowledge, helping to point us in the right direction or helping to refine the objectives of the magazine.

Jean-Claude Marshall
Director, Clinical Pharmacogenomics Lab
Pfizer

Matthieu Schapranow
Program Manager, E-Health
Hasso Plattner Institute

Michael Hoffman
Scientist (PI)/Assistant Professor
Princess Margaret Cancer Centre/University of Toronto

Jim Watters
Global Head, Translational and Experimental Medicine
Sanofi Oncology

Dr Carl Smith / Managing Editor
Carl took a deep dive into all things 'Data' in Genomics for this issue. In the main feature he looks at what needs to happen to maintain progress. He also takes a genomic-centric view on Spider-Man 2 in this month's movie review.

Keith Robison / Omics! Omics! And Warp Drive Bio
Keith assess the scenario made possible by portable sequencers, and what needs to happen next. In his day job, he works in drug discovery and is author of the excellent Omics! Omics! blog.

Theral Timpso / Mendelspod
Theral presents the case for long reads being the story of the year in genomics. Theral spends most of his time presenting, Front Line Genomics' favourite podcast series, Mendelspod.

Richard Lumb / CEO
Richard discusses whether medicine, as a field, is ready for patients demanding the use of genomics and establishes the first step in a road map to 'genomics for the masses'.

Laura Rae / Conference Producer
For our pick of the web this week, Laura reviews Mendelspod 'George Church at 60' episode. She is currently putting together the Long Read Sequencing, Epigenetics and Rare Diseases streams for Front Line Genomics Boston.
Genomics England’s Executive Chair, Sir John Chisholm, took part in a public engagement event for the 100,000 Genomes Project. The event took place at Oxford University this October, where Sir Chisholm and his Genomics England colleagues outlined the aim and structures of the project to a public audience. The evening was largely focused on fielding questions from the floor. With questions around patient consent, data policy and outcomes for the project, the panel did a superb job of educating and reassuring the public. Questions kept coming long after the official close of the event. Even with his coat on and ready to leave, Sir Chisholm was still willing to take the time to speak to anyone with a question.
MAJOR PUBLICATION

Genomic Surveillance Elucidates Ebola Virus Origin and Transmission During The 2014 Outbreak

Stephen Gire (Harvard University), and his group, studied the current Ebola outbreak’s origin, transmission and relation to other outbreaks using genomic sequencing techniques.

The study analyses samples taken from patients in Sierra Leone, collected between May and June of this year. Samples were taken at multiple time points for 13 of the patients. The resulting genome sequences were compared to each other as well as previously published sequences. The study found that the Sierra Leone outbreak is due to two genetically distinct viruses that spread from Guinea at the same time. It is believed that the virus was carried over after some patients had attended a funeral in Guinea. The deceased had died of the virus.

The genomic data has been made available for other researchers to use. Five of the papers co-authors contracted the virus and died during the course of this study. The contribution of Mbalu Fonnie, Alex Moigboi, Alice Kovoma, Mohamed Fullah and Sheik Umar Khan, towards this study should not be forgotten.

“AS A STEADY FLOW OF NEW ENTRANTS TRY TO STAKE A CLAIM, ESTABLISHED ORGANISATIONS ARE BEING FORCED TO CONTINUOUSLY IMPROVE AND INNOVATE.”

GENOMICS TAKES CENTRE STAGE AT ASHG 2014

The American Society Of Human Genetics held their annual meeting across the 18-22 of October. Researchers, commercial organisations and opinion leaders descended on San Diego for a week of knowledge sharing and business. The impact of genetic research on mankind, was a strong topic this year. With a lot being shared on genetic testing and genomic medicine. The use of genetic ‘Big Data’ being another key point of discussion. The commercial side of the meeting was dominated by sequencing technology & software, and clinical applications.

In the UK, Genomics England held a couple of public engagement events to gauge opinion and field questions on their 100k Genome Project. As this ambitious project completes its pilot stage, the questions being asked of it are raising some interesting points on how genomics will integrate into everyday life.

Both ASHG 2014, and the Genomics England events, produce some encouraging conclusions. Chief amongst these: genomic research is incredibly strong right now and is supporting a growing market. As a steady flow of new entrants try to stake a claim, established organisations are being forced to continuously improve and innovate. The British public are ready for genomics, albeit tentatively. One can’t help but feel that the next couple of years are going to be ground breaking.

23ANDME LAUNCH IN UK

December saw the launch of 23andMe’s Personal Genome Service in the UK. This is not the first direct to consumer genetic test in the UK, but does have the highest profile. The launch has already sparked interested discussions through the general media.
CANCER GENOMICS CLOUD PILOT Awardees Announced

The National Cancer Institute (NCI) granted its three awards for the Cancer Genomics Cloud Pilot contracts. The goal being to build a system that will enable large-scale analysis of the The Cancer Genome Atlas (TCGA) and other datasets. With the volume of data being generated by high-throughput technologies growing exponentially, the storage, transmission, and analysis has become restrictively costly. These pilot programmes are designed to give access to large, valuable data collections and advanced computational capacity to as wide an audience as possible.

The three awards went to a team from the Broad Institute, the University of California, Berkley, and the University of California, Santa Cruz; the Institute for Systems Biology, SRA International, and Google; and Seven Bridges Genomics.

The project came about following the NCI surveying the grantee community on their most frequent computational challenges. Data access, computational capacity and infrastructure are major roadblocks, and ones that cloud based platforms are ideally placed to remove. With the exponential increase in data collection, a lot of it is being stored in silos. In the case of rare variants, larger sample sizes are required to give appropriate statistical power. It is hoped that these platforms will help to facilitate data sharing and allow for integrated analysis.

Genomic Clouds

Amazon, Microsoft, IBM and Google are all in competition for storing genomic sequencing data. The tech giants are hoping to allow users to focus on their research rather than servers and file formats. Adopting cloud platforms should give researchers more processing power and easier integration.
2014 NOBEL PRIZE WINNERS

Physics – Isamu Akasaki, Hiroshi Amano & Shuji Nakamura
“For the invention of efficient blue light-emitting diodes which has enabled bright and energy-saving white light sources”

Chemistry – Eric Betzig, Stefan Hell & William Moerner
“For the development of super-resolved fluorescence microscopy”

Physiology or Medicine – John O’Keefe, May-Britt Moser & Edvard Moser
“For their discoveries of cells that constitute a positioning system in the brain”

Literature – Patrick Modiano
“For the art of memory with which he has evoked the most ungraspable human destinies and uncovered the life-world of the occupation”

Peace – Kailash Satyarthi & Malala Yousafzai
“For their struggle against the suppression of children and young people and for the right of all children to education”

Economic Sciences – Jean Tirole
“For his analysis of market power and regulation”

PROFILING OF ‘INNER GPS’ AWARDED NOBEL PRIZE

October saw the award of the 2014 Nobel Prize in Physiology or Medicine. The prize was shared, with one half going to John O’Keefe of University College London, and the other half to May-Britt Moser and Edvard Moser of NTNU - Trondheim. Their discovery of a positioning system in the brain, has been described as an ‘inner GPS’, that makes it possible to orient ourselves in space, demonstrating a cellular basis for higher cognitive function.

John O’Keefe described the first part of this system in 1971. Observing nerve cell action in rats, he found that certain ‘place cells’ form a map in the brain. In 2005, the Norwegian pair of May-Britt and Edvard Moser presented what they termed ‘grid cells’, that allow for precise positioning and pathfinding. They also described a framework within which place and grid cells work together to enable navigation.

How we build up an accurate representation of the physical world around us, is a question that has occupied philosophers for centuries. When you consider the physical world around us, and our ability to map it and navigate through it in our minds, the work of this year’s winners is a remarkable deconstruction of one of the world’s greatest navigational computers in existence.

This discovery represents a key step in our understanding of cognitive processes. Demonstrating the cellular basis of complex navigation may help our understanding of other cognitive processes. Navigational prowess is often affected in the early stages of Alzheimer’s. This breakthrough may help our understanding of this disease in particular.

John O’Keefe is Professor of Cognitive Neuroscience at University College London’s Department of Cell & Developmental Biology. His research group is interested in the function of the hippocampal formation and, in particular, its role in spatial behaviour and spatial memory. He received his PhD in Physiological Psychology from McGill University in 1967.

THEIR DISCOVERY OF A POSITIONING SYSTEM IN THE BRAIN, HAS BEEN DESCRIBED AS AN ‘INNER GPS’, THAT MAKES IT POSSIBLE TO ORIENT OURSELVES IN SPACE,”
MENDELSPOD INTERVIEWS GEORGE CHURCH AT 60

Harvard Medical School’s acclaimed Professor of Genetics, George Church, joins Mendelspod to discuss his appearance on Colbert, Long Read Sequencing and his 60th Birthday bash.

Church recently published his book, ‘Regenesis: How Synthetic Biology Will Reinvent Nature and Ourselves’, which strives to dissolve the line between nature’s achievements and what we might hope to achieve through engineering. Whilst travelling the circuit promoting his book, Church attracted a lot of attention for presenting Stephen Colbert with 20 million DNA copies of his book on a thin slip of paper. One of the largest surprises for Church since publishing the book is that there are a number of companies and libraries interested in applying this approach to solve their own archiving problems - an area his lab is still working on today.

This is not the first time George Church has faced the media spotlight. In 2013, he was the subject of a media storm after several tabloids misquoted him following an interview with Der Spiegel. When asked about the incident George gives a little chuckle. He reflects that the tabloid had been going for a style of headline similar to ‘The Onion’, but that the public didn’t receive it as such. He uses this as an example to advocate the need for technical decision making to be incorporated into education.

Continuing to champion the need for public engagement, he raises some interesting points when answering an audience question about the backlash regarding GM crops. George believes that the failure for this to be accepted lies partly with the lack of engagement and education and contrasts this with the comparative acceptance of gene therapies. Which he believes is what should have led the public perception of the GM revolution.

Mendelspod then puts another audience question forward - this time asking how much big data will affect the training of future biologists. George carefully considers this, emphasising that there are many ways for a scientist to be great and that the average researcher isn’t likely to be a high language coder. Whilst he says that deep knowledge of math is not a prerequisite, he finds it can be very helpful when it comes to having intuition in the lab.

The topic of big data is an enormous one, and from one huge topic to another - George is asked whether Long Read Sequencing will be the next big story for NGS. Church affirms its importance and highlights the market success of Pacific Biosciences sequencing despite a comparatively high error rate of 15%, which he suggests can be compensated for with good coverage. Predicting the potential for a disruptive technology - George talks about Nanopore and suggests that with it’s cheap and portable appearance, it’ll open the door to fantastic new applications if it drops it’s error rate from the current 30% to under 15%.

As the title of this podcast suggests, George Church is indeed 60 - So how does the world famous geneticist/technologist celebrate his birthday? Surrounded by a group of 190 peers who gathered together for a ‘bogus conference’ to celebrate Church’s birthday and to discuss science, engineering, and the future of the field. Many would find this an unusual way to celebrate, but for a man who believes that his research, business and art are so interconnected that they’re more of a hobby than a job, it seems to be the perfect party. ■ Laura Rae

WHILST A DEEP KNOWLEDGE OF MATH IS NOT A PREREQUISITE, HE FINDS IT CAN BE VERY HELPFUL WHEN IT COMES TO HAVING INTUITION IN THE LAB.

George Church
George Church is Professor of Genetics at Harvard Medical School, and Director of PersonalGenomes.org, which provides the world’s only open-access information on human Genonomics, Environmental & Trait data. His innovations have contributed to next generation genome sequencing methods, as well as various applications spanning medical diagnostics and synthetic biology. He has also pioneered new privacy, biosafety, environment and biosecurity policies. He is director of NIH Center for Excellence in Genomic Science.
WELCOME TO THE SEQUENCING-ON-THE-GO ERA

PORTABLE SEQUENCING IS NEARLY HERE. WITH THE SIZE OF SEQUENCERS SHRINKING, WHAT ELSE NEEDS TO HAPPEN BEFORE WE CAN START SEQUENCING-ON-THE-GO?

A

utumn in New England brings with it many annual rituals. It is time to visit orchards and pick apples, invariably ending up with a bag of many varieties but no memory of which apples are which cultivars. It is also a time to clean up the garden, and try to remember which woody plants are deliberately planted ornamentals and which are “volunteers” brought by wind, birds or squirrels. If only I could read the DNA in each fruit or twig, then I might have a reliable guide.

Those wishes may be mostly whimsy; far more serious is the Ebola outbreak raging in West Africa and trickling into Europe and North America. Better biosurveillance might possibly have detected the virus earlier, perhaps leading to more rapid containment.

Historically, DNA sequencing is a scientific exercise performed with expensive equipment in well-stocked laboratories. From 1 meter long electrophoresis plates to bench-sized instruments, it has not been easy to rapidly move DNA sequencing capabilities to the field where they may be wanted or needed. Ion Torrent instruments are routinely advertised using a fully-equipped laboratory on a bus, and more recently reports have emerged of Ion Torrent laboratories mounted on small ships. Those are important steps, but what if an entire sequencing lab could fit in a set of large suitcases, or better yet in a backpack?

An important step in that direction is represented by the Oxford Nanopore MinION, available to a select set of researchers world-wide as part of an early access program. While these groups try to wrestle consistent performance from the single-molecule instrument, anyone can start dreaming of how to use it if/when those pioneers succeed. The MinION itself fits in the palm of a hand, requiring only a laptop with an Internet connection to supply power and transmit raw data to a cloud-based base caller. The performance has been variable and not comparable to existing systems. However, MinION is only the final experimental step in the process; some sort of nucleic acid sample must be purified and then converted into a sequencing library for this instrument.

As written, the MinION library process still requires some heavy equipment, but not much. For genomic DNA, shearing by centrifugation through Covaris g-tubes followed by a small number of molecular biology steps requiring incubation, using reagents that must be kept on ice. Importantly, all of these steps are in small volumes and the instrument requires very little sample, meaning there is little in the way of reagents or waste to transport to-and-from a remote site. Making those steps field-friendly is quite plausible. For example, the Do-It-Yourself biology community has demonstrated adaptors enabling common battery-operated drills to serve as simple centrifuges, and DNA shearing using just repeated pipetting is a long-established procedure. Alternatively,
Oxford Nanopore has discussed publicly a MinION concept in which the entire library preparation process within the sequencing flowcell. Temperature control will probably require more work, but perhaps we are closer than we think. A colleague frequently points out the incongruity of shipping thermostable polymerases on dry ice; why must a highly purified enzyme that functions effectively in near-boiling water be kept well below freezing? Lyophilized enzyme mixes have become common as well. For components or steps requiring temperature control, battery-operated Peltier devices would seem a path worth exploring.

Upstream of the sequencer, the nucleic acids to be analyzed must be liberated and/or purified from their biological source. For example, surveillance of bacterial disease might involve PCR amplification from environmental samples, which in turn requires lysis of those samples. Ebola has an RNA-only lifecycle, necessitating (at this time at least) conversion to cDNA. As with the library preparation, easily portable and field capable instruments don't exist because there hasn't been much reason to invent them.

This suggests the question of what is needed in a rapid response or field-deployable sequencing operation. Should it simply enable a team to easily set-up anywhere in the world with electrical mains and fast Internet, or should it truly mean a device that can exist in the field, perhaps running off a campfire-powered thermoelectric device? When I was young, the first personal computers appeared, with the revolutionary idea that anyone could transport a computer to a new location, albeit via loving packing and some awkward hauling of crates. Before long, Adam Osborne brought the concept of a luggable computer, requiring wall power and some serious lifting, but little more. This would be followed quickly by truly portable machines with onboard power and ultimately today's tablets and smartphones. Will DNA sequencing simply skip some of those intermediate steps and leap directly to operating anywhere, or will a more gradual transition unfold?

Oxford Nanopore is unlikely to be alone in this space for very long; as a bevy of startups are promising similarly portable concepts, some of which might even work on naked DNA without any library preparation. An era of sequencing-on-the-go beckons! Scientific opportunities await that were previously impractical. If you could take a DNA sequencing lab anywhere, where would you go?
Next Generation Sequencing transformed the field of genomics. The successful development of the technology opened the floodgates, prompting a flood of genomic data collection. Sequencing became faster and cheaper, making it an even more powerful research tool.

None of this would have happened had it not been for the efforts of a small company spun-out from Cambridge University called Solexa.

Nick McCooke is the man behind the commercial success of the company. He kindly took some time out from driving another genomic revolution at DNA Electronics, to speak with us and reflect on those early pioneering days in Cambridge.

FLG: It seems that you have developed a habit of being involved with very exciting companies at the right time. How did you first become involved in Genomics, and what lead to your move from Rapigene to Solexa?

NM: Rapigene was one of the first wave of SNP genotypers and the CEO of its then parent company, Chiroscience (which had acquired Seattle-based Darwin Molecular), was looking for someone to build the company. I was approached by their headhunter. It was a completely new field so they couldn’t really go to anyone and say “you seem to have exactly the relevant experience”. I guess I was the closest they could get! Anyway, for various reasons, the job came to be one of selling the business, which I did to Qiagen, and then I came back to the UK with some time on my hands. I was approached by John Berriman of VC, Abingworth, which had been funding the work in Shankar Balasubramanian and David Klenerman’s labs in Cambridge University, about becoming CEO of the nascent Solexa. John was one of the first to have the farsightedness to see the opportunity. I guess my experience of developing the SNP genotyping platform at Rapigene was fairly relevant. I met Shankar and David, it seemed a brilliant idea, though still largely at the conceptual stage, and I got offered the job.

FLG: You are very proud of your time at Solexa, and are widely known as the man who built and led the team that pioneered Next Generation Sequencing (NGS). What was the feeling around Solexa at the time that you joined?

NM: Well I’m immensely proud of the team. Our paths continue to cross and it gives me great pleasure to see how their careers have developed from the springboard of Solexa. I joined right at the beginning of it becoming a ‘real’ company and I think we experienced what every radical new idea experiences, a lot of scepticism! Now we have such a thing as NGS, any new player gets a certain amount of credibility just because we know that generally these things can work, but back then it was hard to persuade people that there was something beyond Sanger sequencing. One of the first things I encouraged was a calculation, based on a number of assumptions, of what this massively parallel approach could theoretically achieve. We comforted ourselves that even if we were quite a few orders of magnitude off, we still had a revolution on our hands. Beyond that, it was about organizing ourselves very effectively, building a great team, and creating the sense we were working on something very special – a once in a lifetime experience. Despite the inevitable setbacks along the way, we retained the belief we could succeed.

FLG: Solexa’s story is a great inspiration. There is a constant flow of new university spin-outs forming all the time. Some find success, some never quite reach the same heights as Solexa did. What were some of the challenges that you guys had to face to develop into a commercially viable entity?

NM: Money was always very tight (at least until the NASDAQ listing and move to the US) and we achieved amazing things on a shoestring compared with some of the NGS companies that came after us.
SOLEXA - BUILDING THE NGS DREAM TEAM

Solexa was formed by Cambridge University faculty members, Shankar Balasubramanian and David Klennerman in the late 1990’s with the backing of venture capitalists Abingworth. They put forward their proposal for a 100,000-fold improvement in DNA sequencing technology. Following $23 million backing, Solexa’s first physical lab was set up by Harold Swerdlow in 2001. At this point Nick McCooke joined as CEO, along with medicinal chemist John Milton and bioinformatician Clive Brown (current Oxford Nanopore CTO). This formed the core of the team that pioneered NGS technology leading to Solexa’s eventual acquisition by Illumina in 2007.

Solexa’s technology still forms the basis of Illumina’s current sequencing technology.
FLG: Ultimately, Solexa proved to be very successful and their legacy lives on through Illumina, who are the most dominant player in the sequencing market by a long way. That being said, if you could go back to 2000 and do it all again, is there anything you think you would do different with the benefit of hindsight?

NM: Well if it hadn't worked, I would have plenty of ideas of better ways to do it, but because it did, I can't really suggest we should have done it differently! Like many radical developments, there is at least one moment where everything hangs critically in the balance. The project very nearly failed because of the challenges of reading single molecules. It was rescued by the deal I did with Serono / Manteia to bring in the cluster technology. But that deal itself was an exercise in brinkmanship. The slightest breath of wind in the wrong direction, and the history of NGS would have looked very different!

FLG: It's been nearly ten years now, since you were at Solexa. In that time, what would you say has been the biggest advancement in the field of genomics?

NM: The biggest advance is the ubiquity in the use of NGS in biomedical research and its progression into the clinic!

FLG: With the race to the $1,000 genome, the price of sequencing fell very quickly. With so much available data out there now, it seems we are faced with a bottleneck from an analysis and interpretation perspective. Creative bioinformaticians are a prized asset at the moment, and there is a lot of demand for more user friendly interfaces, and easier to understand analytical outputs. Is there enough of an incentive out there at the moment, to address those problems?

NM: Well I think the best incentive is the market and if you have something that unblocks a bottleneck, makes the process more efficient, you will find customers. In sample prep too, I think there are great opportunities for innovators.

FLG: Genomics, as a field, offers a lot of potential and hope to patients. NGS has been a big enabling technology in advancing this research. At the moment you are serving as CBO at DNA Electronics. From your website, the following quote catches the eye “From scalable semiconductor sequencing to rapid, portable molecular diagnostics, our mission is to enable and develop fast and user-friendly products with wide-reaching and high-impact applications in healthcare and beyond.” There’s already a growing buzz around DNA Electronics, but I don’t think everyone appreciates just how wide scoped your vision is, in term of broadening the scope of genomic applications. What does the future of genomics look like for you, and what is DNA Electronics’ role in that?

NM: What makes a good clinical diagnostic sequencer isn’t the same as what makes a good research sequencer. We’re much more interested for example in the cost per test, not the cost per base; we’re interested in time to actionable result, not sequencing efficiency; we’re interested in simple sample-to-answer usability, not a flexible non-integrated workflow; we’re interested in targeted sequence not read length. Performing sequencing and PCR on the chip that directly reads the output is a hugely simplifying set-up that provides the perfect core for a diagnostic sequencer.

FLG: From the sound of things, you’re right at the heart of the next big genomic revolution! Thank you very much for your time. We look forward to seeing what comes next from DNA Electronics, and from one of the most pioneering business minds in the history of genomics.
In a new peer-reviewed study, Pieter Mestdagh and colleagues have performed the largest independent comparative study of commercially available microRNA expression platforms to date.

The authors evaluate 12 platforms using 20 standardized samples. A number of quality measures were evaluated to assess performance in relation to: specificity, sensitivity, reproducibility and accuracy.

Exiqon is the overall best performing microRNA profiling platform, offering the best balance between the four key parameters.
So when Illumina, the dominant player in the sequencing space (it’s said that over 80% of the bases sequenced are on their machines), announced this January that their new X Ten system delivers the $1,000 genome, the news was heralded far and wide.

As we so often hear at conferences, the decline in sequencing costs has far outpaced Moore’s Law, a phenomenon in the high tech industry observed by Gordon Moore that the price of semiconductors falls every two years while the capacity doubles. This summer, Forbes columnist, Matt Herper, named the incredible drop in the cost of sequencing after Illumina’s CEO: ‘Flatley’s Law.’

But Herper’s summer article was already passé the day it was published. The Illumina announcement is not the most incredible tale of sequencing this year. Rather, it’s said that Pacific Biosciences and the rise of long reads. We’ve seen the $1,000 genome becoming a reality for some time. What we didn’t see was that quality would get such a bump this year, a quality which is enabling significant new research into the human genome. For a couple years now it’s been known that the PacBio® system was offering the best de novo sequencing in the microbial space. But this year several of their users have seen a dramatic boost to their work on characterizing the human genome and transcriptome. Average read length on the current PacBio RS II system is around 10-15 kb. Contrast this to the 100 bp reads generated by short read technology such as Illumina’s.

This ability to get much longer reads is opening up new scientific opportunities.

Gene Myers, currently the founding director of the Systems Biology Center at the Max Planck Institute, is best known for developing the BLAST algorithm for sequence alignment back in the 90’s, working on the Human Genome Project at Celera. Then he got out of sequencing to pursue “more interesting science.” The future of sequencing was pretty straight forward for Gene and not that interesting, he says in our recent interview at Mendelspod. “Everything basically went short because that’s where you could get the reduction in cost,” says Gene. “Today everyone does it routinely but I don’t think they should be... They’re using 100 bp reads, and the assemblies are crappy.”

It appears that the questions this year are, if Illumina’s $1,000 genome is done with short reads, then just what are you getting for that $1,000? And furthermore, has the drive to the $1,000 genome proceeded at the expense of quality?

“Yes,” says Mike Snyder, Chair of Genetics at Stanford. “I think people’s eyes are opening to that.”

Mike says that with the $1,000 genome (which he points out is, in reality, a $1,600 genome), “the quality is still not there. There’s still significant gaps.”

Mike and his colleagues published two papers this year on the importance of long reads in his work on the transcriptome. “It is difficult to identify full length transcript isoforms using short reads,” the authors write.
Mike says, “the way we figure out transcriptomes now is kind of crazy if you think about it. We take RNA and blow it up into little fragments, and then we try to assemble them back together to understand what the transcripts looked like in the first place. It’s a horrible way to do this.” Recently at a conference at Stanford, I heard Marc Salit from the National Institute of Standards and Technology (NIST) say that we’ve only been looking at 80 percent of the genome. The other 20 percent, which holds much of the disease linked variants, has been beyond NGS technology. That is now changing with the PacBio long reads.

Dan Geraghty, a researcher at the Fred Hutchinson Cancer Center, has been working on the difficult region of the genome known as the major histocompatibility complex, or MHC. This region controls a major part of the immune system and is linked to many common diseases. Dan says researchers have so far been unable to find causal linkages to common diseases, such as diabetes, celiac disease, and rheumatoid arthritis in the MHC region because they haven’t been able to look at long enough pieces of DNA.

To try and get a complete look at a long genetic region in the past, researchers have used Illumina’s short read technology and then had a lot of data analysis and finishing work to do, explains Dan. Finishing takes hours and hours, and even then doesn’t give an accurate picture. So what about all the human genome sequencing efforts such as the NHGRI’s 1,000 Genome Project or the Genomics England’s 100,000 Genome Project? They’re all being done on Illumina’s short read technology. Shouldn’t researchers be using long reads to get the most accurate data possible?

This brings us back to cost. The PacBio long reads currently cost about ten times the Illumina short reads. But Dan Geraghty still says, yes, discovery projects should be done with the better technology.

Gene Myers of the Max Planck Institute says that ‘technology’ has been the winner this past decade, not ‘science.’

“There was this focus on trying to make sequencing the human genome cheaper,” Gene says. “And we knew that eventually technology would win that one. You didn’t have to be much of a visionary to see that.”

According to Gene, the race to the $1,000 genome has been good for medicine but not for science.

“What we really mean by the $1,000 genome is the resequencing of an individual for $1,000 so we can understand their genotype, so we can do genotype/phenotype correlations. That’s a medical problem,” he states.

But Gene says he’s a scientist and not interested in medicine. He decided to get back
into sequencing again when Mike Hunkapiller, the CEO of PacBio, told him that even though the PacBio read lengths were having high error rates, the errors were random. This meant that when you stack the reads up high enough, you get a very accurate sequence. “You could get Q100 bases [perfect quality] if you were willing to go deep enough,” Gene explains, “whereas with all the other technology to date, you can only get to Q40.” We might say then that the new holy grail in NGS is long reads with high throughput. This would improve scientific discovery and offer a scalable technology for medical applications. “If the long reads are high quality and cheap, you wouldn’t need the short reads... [long reads] would take over the market,” says Mike Snyder.

For now this long read story is pretty much owned by PacBio. But all of these researchers say they are platform agnostic and happy to see new technologies on the horizon that are promising long reads. Oxford Nanopore, Genia and Nabsys are all committed to this holy grail. We’re beginning to hear initial data from the beta users of the Oxford Nanopore MinIon, which is looking encouraging, but the throughput is nowhere close to that of Illumina’s short read sequencers or the PacBio RS II. Genia and Nabsys have yet to produce any real data.

Illumina, too, is offering a long read technology--a kind of long read fix got by some special sample prep and bioinformatics work. But so far the data quality hasn’t been very convincing to any of the scientists we’ve had on the program.

So what does this all mean? Will Illumina’s short reads be used for the massive scaled projects, such as medical work and PacBio’s long reads for scientific endeavor? When the race to the $1,000 genome was first touted, there was widespread enthusiasm that more sequencing would mean better understanding of disease, that we’d find the causal variants within the genome right away. But, according to George Poste of Arizona State University, out of 150,000 biomarkers named in research papers, only about 100 have been commercialized. We’re good with the Mendelian diseases, but not so much with the more complex diseases. Dan Geraghty thinks that our poor ability to characterize certain complex regions and the structural variation of the genome has been part of the problem. He and others are thrilled with the new scientific opportunities offered by the long reads.

“We’re hot on the trail,” Dan says of his research today with the “game changing” long reads. “We’re not looking under the lamp post for the keys. It’s daylight, and we can see the whole neighborhood. So we’re gonna find the keys.”

**“WHAT WE REALLY MEAN BY THE $1,000 GENOME IS THE RESEQUENCING OF AN INDIVIDUAL FOR $1,000 SO WE CAN UNDERSTAND THEIR GENOTYPE”**

Theral Timpson – Theral is Host, Producer & Co-Founder of Mendelspod. Founded in 2011, Mendelspod features interviews with a who’s who of thought leaders from life science research. He has over 15 years experience establishing and growing companies in the life science industry, including President and Co-Founder of Consumer Genetics and Vice President of Marketing at Medax International. He is passionate about science PR and communication.
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The genomic revolution is one driven by technology. Although next generation sequencing technology is almost commonplace now, that was not always the case. Its spread would not have happened without early adopters and advocates. David Smith is one of those early adopters and advocates of NGS technology, and currently chairs the Technology Assessment Committee for the Center for Individualized Medicine at the Mayo Clinic. He uses genomic technologies in his research to understand the molecular alterations that underlie cancer development.

David kindly took some time during his last trip to London to discuss where he feels some of the biggest challenges for genomics, as a growing field, are today.

FLG: What do we need to be talking about, when we speak about the future of genomics?

DS: Think about the time in the not too distant future, where everyone has their genome in their pocket and how that's going to change healthcare. Who's going to be in charge of the information, and how will it change medicine when it's not just diagnostic tests but can I just 'scan your iPhone'? The problem is, that the area is so broad and ill-defined, that no one really knows how we're going to get from here to there. It's kind of scary for a doctor. The sort of testing that they're doing now, in 5 years it will be gone. If you're a patient, you're not going to need to go to a doctor for the sorts of tests that are currently being used in clinical practice. You're going to have to go to a bioinformatician, to make sense of your sequence in the context of your symptoms.

FLG: Where does Mayo Clinic fit in?

DS: Our motto is “the needs of the patient come first”. But no one really has a good vision on where genomics will go. I don't think anybody does. Genomics is going to change every aspect of medicine. You can see it on a small scale already. In the past there was considerable need for cytogeneticists to analyse chromosomes. Already that is being replaced by array comparative genomic hybridization and very quickly that will be replaced by some type of whole genome sequencing. What we really need are bioinformaticians and data storage. Two of the biggest problems in this whole field right now are analysis and storage. Right now no-one really has a clue.

FLG: How do we get from where we are now, to genomics on a nationwide scale?

DS: There are two different issues: what happens in the large centres and then what happens in the regional hospitals? The large centres aren't so problematic. However, a regional hospital can't have the infrastructure that say somewhere like the Mayo Clinic has. So we have to look at the model that works best for the populous rather than the bigger centres. Most places can't afford the infrastructure, so they need a model which gives them the best provider so that they can send stuff out to get analysed and get it back in a form that's digestible. You can't get back an encyclopaedia of alterations; you just want something that tells you which drug to give the patient.

FLG: Is there a negative pressure on healthcare?

DS: I don't know if it's negative, but if you can't predict the future it's kind of scary. Medicine was much more comfortable when
MAYO CLINIC

Mayo Clinic is a non-profit medical practice and research group based out of Rochester, Minnesota. It is the first and largest integrated non-profit medical group practice in the world, employing more than 3,800 physicians and scientists, and 50,900 allied health staff, specialising in treating difficult cases through tertiary care. The practice was originally founded by Dr William Worrall Mayo in 1864. The original practice was developed into Mayo Clinic by his sons. U.S. News & World Report, recently ranked Mayo Clinic as the best Hospital in the country for 20014-2015. It is widely regarded as one of the world’s premier medical centers, particularly respected for its approach towards integrated care.

MOST ACADEMICS TEND NOT TO INTERACT WITH THE BUSINESS WORLD, BUT IF YOU CAN GET THESE PEOPLE UNDERSTANDING EACH OTHER, JUST THINK OF SOME OF THE POTENTIAL FOR INNOVATION AND SPIN-OFFS

FLG: Where is your focus on at the moment?

DS: I’ve focused on next gen sequencing. It’s going to be a diagnostic for the cancers I research, and most cancers actually. So now we need to figure out how we get it across to doctors so they know that it’s cheaper and more informative. But of course it has a lot of challenges, which are again, analysis and storage.

You get comprehensive information, but how much are you supposed to tell the patient? That’s a huge problem. But it does also change the paradigm.

There are now discussions now across the board in genetics to train a whole new group of people. Because even genetic counsellors now don’t have the tools to deal with this. So what will this new group look like? Bioinformaticians don’t understand the biology or the clinic; so do we need a new type of person with...

FLG: Where is a good place to start making an impact?

DS: Education. Make more people aware of the revolution that’s occurring. And out of that comes contacts, people getting to meet each other. Getting people together that normally wouldn’t meet each other at all. Most academics tend not to interact with the business world, but if you can get these people understanding each other, just think of some of the potential for innovation and spin-offs. It’s all about finding a sweet spot! But it’s really broad right now. A lot of people are trying to focus in. However, even just looking at NGS for cancer, or drug development, or companion diagnostics, are still really broad.
both types of expertise, or a new system where they all work together somehow?

**FLG:** Where do you think the big breakthrough is going to come from?

**DS:** I see a lot of meetings in the United States. But it’s interesting to see Europe. There’s a dramatic difference between the United States and Europe. The UK may not have as much money, but you’re smaller and more nimble. I’ve seen a lot of efforts from small places in Europe where they’ve been able to turn on a dime. But I don’t think anyone is really prepared. It’s going to shock a lot of people. But the good news is, these tools are extremely powerful and are going to start being used. The key is to look for the low hanging fruit.

The lowest hanging fruit is Cancer. We waste hundreds of thousands of dollars on treatments and cures that only work on 10% of the people. So if we can work on that and optimise that, it’s a great place to start.

**FLG:** How have you seen the field change over the past few years?

**DS:** Next Gen Sequencing isn’t just in cancer, it’s everywhere. 5-10 years ago, when I was talking about this, people didn’t believe me. So it’s nice to be proved right about something! But there are still problems, and no one has any clue how to integrate data. It’s not just whole genome sequencing. It’s RNA seq, methylation sequencing, and how do you put all of that information together? I haven’t seen anybody in the whole world who knows how to do that. Integrating data is a key topic right now.

At the moment, we’re definitely in the educational stage. When I went to the first Illumina User’s meeting 4 or 5 years ago it was Washington University and the big sequencing units that were doing it, and attending those types of meetings. Now everyone from everywhere is starting to get involved in this technology and attend these meetings. In basic research, for example, if you write a grant and you don’t have next gen sequencing in there, you’re not competitive.

**FLG:** Is increased involvement from a major player in the data business, like Google, an encouraging sign?

**DS:** We need more investment in data analysis, so having Google and IBM starting to think about it is a good thing. We need more help. A lot more help. The current NIH funding model is abysmal. If we can get Bill Gates or some of those guys’ interests it’d help a lot. So having Google involved is a big plus.

**FLG:** How far can you go with that level of mathematics and computer science without the domain science to support it? That’s one of the criticisms around Bioinformatics at the moment.

**DS:** It’s one of the biggest problems. They’re so obsessed with mathematical models that they can’t fathom the biological question. We need to start training people who understand computers and bioinformatics, but within the context of a disease. I see some of the best places in the world with some of the best bioinformaticians, but they don’t understand the biology of the disease.

**FLG:** So with the field changing so rapidly, how does your working life change?

**DS:** Firstly, I have to struggle with funding like everybody else! The other important thing is, I’m just wondering if it’s getting out of my grasp. I liked next gen sequencing a few years ago when you could just do one cancer, analyse it and you had a really big paper. But now, I’m having to rely on the amazing people and bioinformaticians at Mayo to add that extra layer. I wish I could go back and learn it all, but it’s those guys who have that understanding which are going to be in the driving seat. So we might just retire here to London!
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DATA: INTO THE HEART OF THE STORM

DATA IS AT THE HEART OF GENOMICS. WITH THE AMOUNT OF DATA BEING COLLECTED INCREASING EXPONENTIALLY, THERE IS A WORRYING IMBALANCE IN SUPPLY AND DEMAND FOR BIOINFORMATICIANS. WITH ALL THIS DATA, WHAT ARE THE BOTTLENECKS TO OVERCOME BEFORE THE GENOMIC ERA CAN TRULY BEGIN?
DATA

OF THE WORLD’S DATA WAS GENERATED IN THE LAST TWO YEARS.

This statistic is often the starting point of any conversation on data, and is so often used that it is now out of date. The volume of data being collected keeps increasing, so the relative proportions will likely be a little different as we approach 2015. Regardless, data is increasingly becoming an important part of everyday life for all of us. Perhaps the most obvious application of data driven insights, is in our shopping experience. We are presented with suggested products and coupons based on our shopping habits referenced against a library of similar transactional journeys. This is the world in which we live. A world in which how well you can read, and leverage, data will define your success.

THE WORLD OF ‘BIG DATA’

Big Data, is a term that has proved difficult to define. Edd Dumbill, of Silicon Valley Data Science, has been writing, organising and developing around Big Data since the beginning. His definition is as follows “data that exceeds the processing capacity of conventional database systems. The data is too big, moves too fast, or doesn't fit the strictures of your database architectures”. He also notes that, where information systems used to be confined to the back office, they are now forming the backbone of business value creation. He also insists that any company has Big Data. The problem is that a lot of us discard what doesn't fit our traditional or conventional systems. To thrive, organisations need to understand the “new canvas on which they’re painting”.

90%
The process of digitisation is one that we are all going through. In our personal lives, we are adopting smartphones, e-readers, tablets, MP3 players and more. That’s not even mentioning the wave of wearable devices and the Internet of Things revolution on the horizon. In a business setting it’s much the same. The biggest change being in how we house information and moving towards cloud computing.

Digitisation is more than just a time saving exercise. Success is found by realising what digitisation allows you to do that you could not do previously. This is something that sits at the very heart of genomics. George Church and Sri Kosuri, of Harvard, managed to cram 700 terabytes of data into a single gram of DNA. That makes DNA one of the world’s densest storage media, by a very long way. Sequencing technology has developed such that the raw data can be read. Translating that into useable information is the work of thousands around the world. Identifying genes, looking for interactions, understanding gene expression, finding correlations with particular phenotypes...There is a lot of work that goes into making that raw data mean something.

John Quakenbush, of the Dana-Farber Cancer Institute and Genospace, on partnering with Thomson Reuters to build a new gene variant database, stated “the barrier to establishing personalised medicine is no longer generating data, but analysing and interpreting it.” Taking that raw sequencing data and adding in that contextual layer of detail, and using it as a reference tool, as well as as an exploratory tool in its own right.

**BARRIERS:**

**PEOPLE**
Talented data scientists are a precious resource. These are the people that are building the algorithms that mine genomic databases, transforming high-dimensional functional data into interpretable patterns. In essence, this is what will fuel the Genomic Era. Sir John Chisholm, of Genomics England, proclaimed “This is what is going to change the experience of mankind”, last month at a public event addressing the 100k Genome Project. He was referring specifically to applicable insights that will result from the kind of databases that they are building.

As the field of genomics grows, its data-centric nature means that bioinformaticians are in high demand and short supply. In its present state, modern bioinformatics is a comparatively young field as it has developed alongside the technology it relies on. In speaking with research institutes and Big Pharma, the comments are consistent: “I wish I could find more people who can do this stuff”. The need for people with this particular cross-domain skill set is already being addressed. With several graduate programmes already in place, IBM’s Big Data Evangelist, James Kobielus, is predicting that data science is going to continue to filter down the educational system until it forms part of the high school curriculum. In decades to come it may simply be that the computational work becomes less isolated, as people have a much stronger basic capability to carry out the analysis themselves. At this point, technical proficiency would not be the limiting factor. Instead it would be a case of having the creativity and scientific understanding to apply those computational skills.

**STANDARDS**
The personnel shortage is only part of the problem. The lack of deep, and widely accepted, data standards is a problem. Keith Bradnam, of the UC Davis Genome Center, frequently interviews bioinformaticians on their perspective on the field as part of his ‘101 questions with a bioinformatician’ series. When asked what is one of the less appealing parts of being a bioinformatician, Michael Hoffman, of the Princess Margaret Cancer Center, explained “The amount of time wasted by moving data around, converting it from one format to another.” This follows from a, now infamous, tweet by another prominent member of the field, Nick Loman, of Birmingham University “Bioinformatics... Or ‘advanced file copying’ as I like to call it.”

This is a recognised problem, and one that is taking time to be addressed. There are various groups looking to develop appropriate standards, most notably the Global Alliance. The importance of standards cannot be over stated. Beyond the practical benefit of eliminating a mundane task, they also allow for much greater interoperability and integration. From an organisational perspective, it also reduces the risk of potential vendor lock-in.
PAPERWORK
Speaking on his work with The Cancer Genome Atlas, David Haussler of University of California, Santa Cruz, says that the technical challenges of integrating so many different types of data at such a large scale are easily surmountable. He has found that the bureaucratic processes involved in collating and housing all this data was overwhelming.

The compliance, security and regulatory environment around the sharing of this kind of data is very dense. This can often trail back to the level of consent a patient has given over the use of his or her data. For example, if a cloud based service provider is to used, patients need to be approached and asked for consent to upload their data to the cloud. Cloud based data security is something that is coming under heavy public scrutiny at the moment in light of some high profile breaches.

EDUCATION
The need for education is widespread. That it is so often called for, is a testament to the potential of applicable genomics to improve people's lives. There are three areas in which education is critical. Research & development, healthcare, and the general public. Each group is a key component of realising a genomic era.

For those working in research & development, cultivating an understanding of genomic tools available and how to incorporate genomic information into projects is an ongoing process. In particular, being able to robustly analyse, and accurately interpret, data.

TRAINING BIOINFORMATICIANS
Universities are starting to develop specialist programmes in an effort to develop people with highly desirable computational skills and scientific domain expertise. University College London’s CoMPLEX (Centre for Mathematics, Physics and Engineering in the Life Sciences and Experimental Biology) is an eye-catching example. Here, MRes and PhD students are supervised by a cross departmental team drawn from life sciences and mathematical/physical sciences. Students are given a founding education across the range of sciences and computational methods they will be exposed to, but the main focus is on developing interdisciplinary research skills.

Interestingly, students from CoMPLEX typically remain in research following completion of their PhD. Their skills are in demand, and have crucial experience across a breadth of applicable sciences. This is in contrast, to ‘domain specific PhD graduates who often look outside of research to make their mark on the world.

Centres like CoMPLEX, show that leading institutions recognise the importance of finding innovative approaches to scientific discovery. Which is indicative of how research in the life sciences is changing.

James Kobielus, IBM’s Big Data Evangelist, believes “computational tools accelerate discovery, if applied correctly”. They are becoming an increasingly significant aspect of research, with Kobielus predicting that “a computational method will win the Nobel Prize [in physiology or medicine] in the next few years”.

If Big Data is about storing and moving big data sets, Bigger Data is about using that data and turning it into information.
Equally as important is the need to understand how to integrate these tools at an organisational level and ensure that necessary infrastructure is in place to fully exploit them.

Healthcare is where the majority of the population will come into contact with genomics. This places a lot of responsibility on healthcare professionals to ensure that it is a positive experience from the outset. This means that point-of-care professionals need to be fully aware, and informed, of their genomic options, such that they can recommend them and explain them adequately to their patients. This will also heavily rely on healthcare policy, and insurers, to appropriately reimburse for these treatment options. Once again, this is another area in which interpretation of genomic data analysis is of paramount importance. Where medical recommendations are being made, a physician needs to be sure that he or she fully understands the results of genomic testing to make a confident recommendation.

Patients are the group that exert the most pressure. This is ultimately what will drive a lot of the progress in integrating genomic healthcare. For this to happen, there is a significant amount of education that needs to take place. A lot of this is raising awareness, and dispelling misconceptions. This ranges from basic genetics through to addressing security issues around data on the cloud. Where a deeper level of education becomes more important, is when a patient is facing the prospect of being involved in a clinical trial, or receiving the results of a genomic test. Understanding what happens to their data, and what their results are telling them is crucial in getting patient buy-in and managing expectations.

Hype is a dangerous thing. The importance of managing public expectations must be stressed. Finding novel therapies is a complicated and time consuming process. But in the short term genomic research, will help to develop our understanding of diseases, offering improved diagnosis and care options. This is a point that Mark Caulfield, Chief Scientist at Genomics England is keen to stress. As important as it is to raise genomic awareness, it is equally important to manage public expectations.

**LOOKING AHEAD**

How we use genomic data, is what will ultimately “transform the experience of mankind”. Increasing our understanding of diseases, will lead to better therapies. It will also lead to far superior diagnostics to identify the best course of treatment. But is that what will really transform the experience of mankind? The probability of developing a form of invasive cancer is extraordinarily high. Statistics from the US National Cancer Institute’s Surveillance Epidemiology and End Results Database, suggest that 1 in 2 males and 1 in 3 females will develop cancer. However unfortunate it may be, cancer is an unavoidable part of the experience of mankind. Either you will get it, or someone very close to you will. On those terms, it is easy to see why Sir John Chisholm is so confident that the field of genomics will have such a transformative impact on us all.

Sequencing technology is no longer a bottleneck, but new developments are going to be very interesting. Illumina President, Francis de Souza, estimates 1.6 million genomes to be sequenced by 2017. But what might that number look like by 2020? Sequencing sits firmly in the realm of research, for the time being. That is already starting to change, as it moves into the clinic and beyond. Oxford Nanopore’s MinION is already capturing the imagination (as evident in Keith Robison’s piece in this issue). Having a sequencer the size of a USB stick opens up a lot of new applications outside of disease research. DNA Electronics, are another company innovating in this space with their Genealysis chip.

The Genealysis chip is working towards becoming a handheld diagnostic too for point-of-care healthcare workers. DNA being the input, and a simple YES/NO answer being the output. At present the chip is being used in the cosmetics industry. Customers can have their DNA quickly analysed to match them up to the best anti-ageing cream for them. This may sound like a dubious application on first glance, but it does offer a useful application that will help develop the technology. The regulatory landscape for diagnostic medical devices is complicated. In addition, there is still an element of fear of the unknown for the public. Genealysis creator Christofer Toumazou, says the following “What I’m trying to do is bring medical-grade
technology to the consumer and, in this particular way, actually bring personalised medicine to the beauty industry. "[We’re] taking the stigma away from the medical device. [We’re] getting the consumer to see and accept the fact that a genetic test is not a big thing.”

Creating these non-threatening touch points between genomics and the public are going to be critical in the education process. More interestingly though, they may also help provide some interesting genomic data along the way. Data is at the heart of genomics. Everything good, will come about from how that data is exploited and interpreted. Before too long, we might find that data is not only at the heart of genomics, but at the heart of healthcare. Connected health is coming, and with it will come the ‘tsunami of data’ that we often read about. Wearable devices are starting to grow in popularity. Coupled with the Internet of Things revolution, we are going to be faced with a lot of new data sources. Combining, genomic data with deep lifestyle data and accurate healthcare records opens up the possibilities once more. That is also the point at which we start to talk about ‘Bigger Data’.

**BIGGER DATA**

If Big Data is about storing and moving big data sets, Bigger Data is about using that data and turning it into information. Above the relatively simple storage issues, the problem turns to making sure we have a common index between datasets being compared. With the potential to look at several different types of datasets in addition to genomic databases, this can become a difficult and time consuming problem to overcome.

**A BRIGHTER FUTURE**

Genomics has the potential to help people live longer, happier, lives with not only cancer, but many other diseases. The contribution of bioinformaticians to this cannot be overstated. There is still a long way to go, but the good news is that the limiting factors are easily identifiable and are already being addressed. The lack of standards, and shortage of bioinformaticians, is a direct result of success. No clear standard has emerged, because there are so many successful groups and projects out there working with different platforms. From a technical perspective, there are several solutions to a single problem. Now we just need to find a way to better integrate those solutions.

The personnel shortage is worrying, and encouraging at the same time. It is worrying because it is creating a bottleneck that will slow down progress. The encouraging aspect of this, being that demand for bioinformaticians is high because of the importance of their work. Simply put, more people want them. In 2014, Professor Hoffman is having a tough time “finding enough people who can do this stuff.” By 2020, people won’t be struggling to find people with the right skills, they will be trying to identify the very best from the masses of applications they will be fielding. Hopefully.
Data is at the heart of genomics. But, there is no data without people who are willing to be sequenced. Most will have their first contact with genomics through participation in a research project. How they engage, and interact, with genomic information is going to have a significant effect on how the technologies will be integrated into healthcare. Despite strong discussions, there is startlingly little data to help guide the ethics and policy around the reporting of such information back to patients.

Dr Anna Middleton, of the Wellcome Trust Sanger Institute, headed up an extensive ethics study as part of the Institute’s ‘Deciphering Developmental Disorders’ project. This produced the world’s first large scale empirical data, giving all sorts of people (from patients through to scientists and health professionals) a voice on what they want from genomics. Some of the findings of which, are about to be published in the Lancet.

We travelled up to the Sanger Institute to meet Anna and hear more about the story behind the research ahead of its publication, and what it means for healthcare moving forward.

FLG: How did you first get involved in genetics?

AM: My first degree was in genetics. I always liked genetics, but I knew I didn’t want to work in a lab. So I trained to be a genetic counsellor and I learnt about the communication skills needed to deliver genetic information to patients. What unites people, and makes people a family, is something that’s always been fascinating to me, and is what really drew me in. I’ve been working at Sanger for 4 years as I decided to focus on research full time and have been a full time academic now for 10 years. I’m the only social scientist on the campus, which makes things really interesting and exciting.

FLG: How was your experience as a Genetic Counsellor?

AM: For many years I specialised in breast and ovarian cancers. I worked in the genetic counselling clinic with families who were at risk from inheriting or passing on genetic conditions. They would come and see a genetic counsellor, or clinical geneticist, to come and talk about why a condition is there in the family and what the chances were of passing it on, or inheriting it. I’m used to working with both men and women who have a very strong family history of cancer, who are often very frightened of developing it. We offer genetic testing to work out if there was a known genetic cause to the cancers, if so, then we could offer predictive testing to at risk relatives. What we did was explain all of this and help to contain the emotional context for the family.

I really enjoyed working with patients. It was a really soulful, meaningful, kind of work. But I did get frustrated with the NHS. We have a stretched NHS where not all screening you want to offer, can be offered. I wanted to do the best by patients, but there were times when I couldn’t due to limits on resources.

I was also very interested in research and wanted to explore the evidence base of what genetic counselling was. Why was it effective, and why did it work? So I stepped aside into research to focus on some of those bigger questions.

FLG: In which area did you focus your research?

AM: My PhD is in Genetics & Psychology. I worked for many years with the Deaf community, looking at how they might want to use genetic technology. I discovered that there are many ‘culturally Deaf’ adults who use sign language and have no issue whatsoever with being Deaf. They like being audiologically deaf, they are not disabled, perceive...
themselves as just using a different language – sign language. I discovered that Deaf people often have a strong (genetic) family history and prefer to have Deaf children – to fit with their culture, heritage and identity. My research was the first to show that Deaf adults would consider a genetic screening during pregnancy to see if the baby was hearing, and that a very small number would consider an abortion if the baby was hearing.

That social sciences research was really quite important as it turned everything around. It questioned what we consider to be ‘normal’ and what we use genetic information for. At the time I was doing my research with the Deaf community, I was also working with a team that was looking for the first deafness gene, this was in the mid 90’s. After the connexion 26 gene was identified, the social sciences research really became relevant. That’s what really got me hooked. Trying to understand how people wanted to use genetic technology and realising that they might use it in ways we didn’t expect, was fascinating.

**FLG:** Which project are you involved with at the Sanger Institute?

**AM:** I came here to Sanger to run ethics and social sciences arm of the DDD (Deciphering Developmental Disorders) project. The main molecular arm of the project is a really lovely collaboration between the NHS and Sanger Institute. For kids with really severe developmental disorders, who have not been able to get a diagnosis through the NHS, they are now able to get an exome sequence as part of the research project. It’s allowing these patients access to the technology that they wouldn’t get on the NHS, which is great. We’ve currently got a diagnostic rate of about 31%. So in these families where there was no diagnosis, about a third now have a diagnosis and that is entirely due to the sequencing they have got from the Sanger Institute. This project is really about working through the science and making it very clinically focused and providing an answer for these really vulnerable families.

**FLG:** I really enjoyed working with patients. It was a really soulful, meaningful, kind of work. But I did get frustrated with the NHS. We have a stretched NHS where not all screening you want to offer, can be offered.
By having the sequence you have an awful lot of other information in there; information that could be of interest but has nothing to do with the developmental disorder. That presents an ethical conundrum: what do we do with all those other things that we're not actively looking at? For example breast cancer genes and Alzheimer genes. The decision at beginning of the DDD project in 2010 was that we would not explore any incidental findings. At that time such incidental findings were not being actively looked for in clinical practice, so it was premature to be doing it in the research setting. I was brought in to create and run a social sciences research project to gather attitudes towards searching for and sharing incidental findings in a research context.

**FLG:** How did you go about collecting that kind of data?

**AM:** At the time, there was no empirical data to say what people actually wanted. There were a few small studies, but nothing on a really big scale across many different countries.

This place, Sanger, is a place for big data on a scale you can only imagine. As a social scientist I was used to working with samples of maybe a thousand, and that was big in terms of social science! So when I came here, I wanted to match the scale. To get a large sample size I knew I had to use a survey rather than conduct interviews. The survey had to be online and I needed to find an innovative way to engage with people. I decided to work with a filmmaker to make ten short films to sit within the survey. The films explained the ethical issues raised by sequencing technologies and then we asked people to answer questions around those issues. We needed the survey to go viral to get the volume of data we wanted. How to get something to go viral is a bit of a mystery. So I worked very hard at promoting the survey but also I think the films really made it something different – more of a learning experience to enjoy. I wanted people to think "this is interesting, what's it all about? I'm intrigued..." and in the end, that's the effect it had. Channel 4 news picked up the issues and ran a really nice news piece about the research, this gave us a great head start and the survey took off from there. After I cleaned up the data, we had about 7,000, good quality, completed surveys from 75 different countries and a really nice spread of social and economic backgrounds. It really took off in a way I hadn't imagined. It was designed as a piece of research, but it's turned into a public engagement exercise. The actual survey and the films are now being used to teach genomics all around the world to medical students, school kids, nurses and anyone who wants to learn a bit about ethics and genomics. Here in England it's now recommended as a resource on one of the A-Level curricula. So even though I've now collected my data and am about to publish, we decided to leave the survey open so people can play with it (www.genomethics.org).

**FLG:** That's an amazing response rate! What did you find in the data?

**AM:** We found out what people want to know from their genome and what they think about researchers looking for incidental findings. The main result to come out of it was that people's attitude was not determined by geography, but determined by whether they were a health professional, scientist of member of the public. The four groups with distinctly different attitudes were: public some with previous exposure to genomics others not; genetic healthcare professionals who worked with patients (clinical geneticists and genetic counsellors); genomic researcher; and healthcare workers who did not work directly with genetics or genomics (e.g. surgeons, nurses, GPs...). But what I found across the board was that people want data. The more useful they perceive the data, the more they want it. Around 96% across all the groups said "If you can tell me information related to an actionable, serious, condition, I want to know that." People wanted actionable data even if the risk of the condition occurring was only very low, e.g. 1%.

**FLG:** Actionable being the key word there?

**AM:** 'Actionable' is pretty hard to define. Clearly you can't present 20,000 genes to someone, so how do you manage it? We categorised the genome into packages of data: variants related to serious or life threatening conditions that are actionable; serious or life threatening conditions that aren't actionable; ancestry data; carrier data; response to medication; and data that's not of any immediate importance but might be useful later in life. As you go through those categories, the less serious they become, there is a correlation between 'usefulness' of the data and interest, the less useful, the interest starts to decline. 'Actionability' is very subjective and participants recognised that it would be helpful for a multidisciplinary team to make decisions about what this actually means for individual conditions, i.e. not just a single bioinformatician or computer algorithm that categorises the data, but a thoughtful process. Participants suggested this could be informed by a collection of different people including a patient representative and ethics input as well as genomic researchers and health professional. Irrespective of this there were still significant numbers of participants who say they want all their data, even the bits that cannot be interpreted and even if it came to them as raw sequence data.

**FLG:** Did people say what they would do with their sequence?

**AM:** Some people were saying they'd take it to their GP, which fills me with concern as currently GPs probably wouldn't have the time or experience to know what to do with a raw sequence! Other people said, "It's genetics, it's me. This is my identity. I just want it. If you know it, I want to know it." Some even said they'd make a piece of art out of it, or put it on a t shirt. People feel very attached to that data and just want to have it. I find that really interesting. I don't think people would say the same thing about an X-Ray of their knee. Genomics seems to touch people in very personal way. Attitudes change when it's something that people freely give out. What are you REALLY going to do with a sequence? We don't yet know if having data really alters behaviours. Some of the early studies done on behaviour change are showing that people are enthusiastic about having data, but still continue to smoke, or don't exercise and don't alter their behaviour significantly. So there is much more needed in terms of psychosocial research on this on what people actually do with genomic data.

**FLG:** Why do you think people have such a different attitude towards genomic data?

**AM:** The perceived 'deterministic' nature of genomic data is something I am very interested in. We all know that most of the data from a genome is not going to be strongly predictive of disease; we also know how hard it is to interpret genomic data. Yet, the public...
perception of 'a gene for...' is prevalent and people feel 'if it's in the genes' then it must be important. If we posed a hypothetical situation... say we suggested you could get data on a serious, actionable, condition. Does the level of risk of that condition occurring change your interest in knowing about it? What I found was that people are very interested across all level of risks. Even with just a 1% chance of a condition occurring, people still wanted to know. Because it was actionable, and people felt that they could do something with it. For me, that's interesting. In the clinical setting, it would be very unlikely to put in a clinical intervention if someone only had a 1% chance of a condition occurring.

Over time, the work will also improve understanding of how genetic changes cause developmental disorders and why the severity of the disease varies in individuals.

For more information visit www.ddduk.org and www.sanger.ac.uk/research/areas/humangenetics/ddd/

that is clinically actionable. I don't want people to just automatically want data as a default response. I want them to really consider whether or not they really want that data, and understand what it might mean for them and how it might be relevant for their children, their parents, their siblings. It could relate to serious things going on in their lives. But even with that caveat, people were still saying yes. They want to know.

FLG: Is there a duty to report findings to patients?

AM: One of the things that has been in the ethics literature for the past 5 or 6 years is the duty to inform people about what they are at risk at. Clearly this exists in the clinical practice, but should it exist in the research context? So we asked survey participants how far they expected genomic researchers should go to deliver incidental findings to them. Most people said that they didn't expect researchers to deliver any results that might compromise or take significant time away from the main research project. So people were able to place a value on that kind of data. They'd like it, but not at the expense of the research. That's a really important finding for the research community, as there had been a lot of pressure from the ethics literature to go down all of these rabbit-holes to provide incidental findings. Our study is the first piece of empirical data that shows that patients don't expect that. That piece of the study is going to be published in the Lancet this December, and the main study is with the American Journal of Human Genetics.

FLG: How does it feel to be the author of a couple of papers that are going to be cited quite a lot over the next few months and years?
**AM:** I'll be excited once I finally see it. It's a big deal for a social scientist. The Lancet doesn't usually publish social science research, so that's a big deal for me.

What's also exciting is that the DDD project that is looking at the sequencing, also have a paper in the Lancet and a paper in Nature that is about to come out. They've discovered new genes through the DDD project, known to be linked to developmental disorders and talk about the translation from the research into the clinic. So that's really exciting too!

**FLG:** How well has the study been received so far?

**AM:** The study has been received incredibly well. I've been around the world presenting it at various international genetics conferences, e.g. in Boston, Adelaide, Milan. I'm very excited that the main study results are about to be published and that the survey has now been translated into Danish and Spanish and is being used by other social scientists to research the attitudes of different populations. I'm also really excited that it is being used in teaching across the world as a model for exploring ethics and genomics. Genomics England also have our survey on their website, to be used as a tool to explore ethics, so it is clearly having an impact in many different ways.

**FLG:** Is there enough being done to help people process the familial implications of genetic data?

**AM:** The family nature of genomics has to be a part of the conversation. Particularly in mainstream medicine. Mike Parker and Anneke Lucassen published a paper where they liken genetic information to a joint bank account where everyone puts something in and everyone gets something out of it (Genetic information: a joint bank account BMJ 2004;329:165). For example: if you've got an individual with a rare disease, that information is going to be relevant to carriers in their external family as well. Individuals often don't do enough to tell their immediate family about what they might be at risk from. The genetic counsellor can help people have those conversations and process those risks. It's important to talk about difficult things with relatives – there might be family that are perhaps quite distant emotionally (but close genetically) so these conversations can be difficult. Genetic counsellors and clinical geneticists are very experienced in supporting patients to communicate with their relatives.

**FLG:** Each case seems unique in its own sense. Can we really form a policy that covers each of them appropriately?

**AM:** We need a good consent process. Where implications of what people are tested for are explained, at least in a broad sense. Broad consent is something that's being discussed in the literature at the moment, especially when you could potentially be looking at 100s of different genes. If people aren't quite engaging at the point of testing, once they receive the result, you work with them a lot more closely to guide them through what the results mean. So taking consent for genomic screening might look different from taking consent for single gene testing. We're also thinking collectively about what this actually looks like. The bottom line is that you don't want to be giving people data that they can't manage or weren't prepared for. So you have to...
do things responsibly and to make sure there is a support structure around them when they do have it. That's one of my concerns around the direct-to-consumer testing market. You're throwing out information to people, and it's only when they get a significant result that they realise that they hadn't done the emotional preparation that they perhaps should have done. This is why I feel it is important in the direct to consumer testing market that there is at least access to a genetic counsellor if people need help – it doesn't have to be an enforced part of the process, but should be available to call upon.

**FLG:** How will we feel the impact of genomics in our lives?

**AM:** It depends on what the genomic technology is being used for. In clinical genetics at the moment most testing is based on looking at one gene, guided by a phenotype or family history. You might choose to sequencing technology to explore that gene Depending on the clinical question, a different approach might be to sequence a panel of genes rather than target one specific gene. Going up another step, it might be more appropriate to do a full genome or exome sequence but have a targeted analysis. So in each case the sequence might be the resource of data and genomic technologies are being used to answer a very specific clinical question or might be offered so that treatment can be personalised. From the patient's perspective they often just want that clinical question answered and are not too bothered about the route to get to that. They may not even know that sequencing technologies have been used nor that a genome is where the clinical information is coming from. So, we might feel the impact of genomics in terms of improved diagnosis and treatment, but we may not be cognisant that it was genomic technology that actually got us there.

**FLG:** There seem to be a lot of concerns around data privacy at the moment. Is that something you looked into?

**AM:** It wasn't a focus of the survey, but the Genetic Alliance have just done a really nice piece of research that they are going to turn into a patient charter. They've asked patients who have already engaged with genomic technology, or who have children with genetic conditions and asked them how they feel about data sharing. They found that patients just want researchers to get on with it. They are much more interested in scientists working hard to find treatments and cures for their conditions, and if this means sharing their data, then so be it. They understand that clinicians and researchers will do their absolute upmost to protect their confidentiality, but for them contributing to medical research is more important.

We tend to get lost in the discussion about data sharing and the possibility of being identified by our genomic data. In reality I think it would be far more dangerous if someone got hold of my bank details than my genome.

**FLG:** With the survey complete, and a lot of work still to be done to bring genomics to the masses, what's the next step for you?

**AM:** I want to do more research that explores the experience of sequencing from the patient perspective. I'm hoping to do some new research in the DDD project on this – trying to unpick the experience of patients with respect to either getting or not getting a diagnosis from the sequencing. There is virtually no research on this, from a psychosocial perspective, at the moment. Building on the survey and thinking about the future, what was really interesting for me was working with a filmmaker and seeing the power of that medium for delivering information about genomics. I'm now tentatively exploring whether it is possible to do this on a large scale. I'm currently scoping out a new piece of social science research that could lead into film creation. My mission is to understand what really connects people to genomics and you don't know until you ask. I want to help people to have a conversation about genomics, bring the concepts into everyday language so that regular people feel confident to chat about at the pub or on the way home from work. In order to do this you need to do a lot of background work to assess understanding and work out how to make genomics inspiring for them. We don't quite know how to have conversations with people about genomics who don't yet know that they need to know it! For many of us at the Sanger, particularly in the Public Engagement team, these are really interesting and important questions. I don't yet have funding for this new work, so if you know anyone who is interested then let me know!
Evaluating DNA sample integrity is critical to sequencing workflows. And no system is better at it than the LabChip® GX Touch. It can handle up to 24 samples at a time, both pre- and post-PCR, for savings of up to 30% in reagent costs. Our unique genomic quality scoring eliminates guesswork, with robust metrics for RNA/DNA integrity. And with our easy-to-use touchscreen interface, even novice users can quantify samples with the best of them. LabChip GX Touch: It's quantification you can count on.
IS THE DELIVERY OF GENOMIC MEDICINE ABOUT TO BE OVERTAKEN BY PATIENT DEMAND?

ALTHOUGH THERE IS STILL A BIG NEED FOR EDUCATION, PATIENTS ARE MORE INFORMED ABOUT THE USE OF GENETIC INFORMATION IN DIAGNOSIS AND TREATMENT THAN EVER BEFORE. RICHARD LUMB DISCUSSES WHETHER THE FIELD OF MEDICINE WILL BE READY FOR PATIENTS AS THEY START TO DEMAND THE USE OF GENOMICS EN MASSE.

Any of us share the same mission: to deliver the benefits of genomics to patients faster. It’s a laudable ambition, but it’s one that is very hard to put into practical steps.

Fundamentally, it comes down to this: From this point in time, what specific steps need to be taken to achieve true genomic medicine? To get to the point where the use of genomic information is relevant and meaningful for the masses. Not just people in the big cities. And not just people with the most money. EVERYONE.

There’s one big over-riding problem: there is no single, universal roadmap for genomic medicine.

A RAY OF LIGHT

Thankfully there has been some great work in the area, particularly coming out of the National Human Genome Research Institute (NHGRI).

Perhaps the most comprehensive outline so far was an article written in 2013 by Teri Manolio et al, from the NHGRI (1). Building from work conducted in genomic medicine symposia, the article presents common challenges, infrastructure and research needs for the introduction of genomic medicine programs into clinical practice.

An earlier influential paper, covering similar ground, was written by Eric Green and Mark Guyer, also of the NHGRI in 2011 (2). It’s perhaps best remembered for describing progress in five different domains of genomic research, the most productive schematic representation of historic and future progress in genomic medicine that I’ve seen to date.

It also simply and accurately describes some of the basic imperatives around not just genomic medicine, but bioinformatics and computational biology, education and training, as well as society.

So why can’t we just put all that stuff into a roadmap, and follow it all the way home?

UNFORTUNATELY IT’S NOT THAT EASY.

I sat down with Eric Green at the recent 2014 ASHG meeting in San Diego. He pointed out to me that we hit surprises all the time. And not all of those surprises are scientific. For instance, there are obvious examples in the policy arena, many relating to the FDA, that have been difficult to anticipate.

In reality, the political, economic, and legal landscape differs around the world. For instance, a 2008 publication from Seguin et al (3) reviewed the situation in Mexico, outlining the requirement to step-up the development of a knowledge-based economy in Mexico. It covered different ground. Not least because the paper also discussed another critical factor: political will.

The formation of Genomics England in the UK is arguably the best-known example of powerful, forward-looking, political will turning into investment and action. Yet political will differs not just across different countries, but also within countries, over any given period of time. Priorities change with governments, public opinion, and available budget.

THERE’S A STORM BREWING

So what does this mean for a universal roadmap that everyone can follow? Well, it means that putting one together is tough.

Amid all of the optimism and excitement around genomics, there are some nasty looking clouds on the horizon.

We’re in an increasingly educated and connected world. Healthcare systems are stretched. Patients and their families no longer solely rely on their doctors for advice. They’re turning to the internet: support groups, patient advocacy organizations, charities, crowd funding, and also scientific literature. They’re looking for support, yes, but also solutions. And hope.

In 2009, my father died of mesothelioma, a type of cancer commonly caused by exposure to asbestos. I started Front Line Genomics because I wanted to understand why progress in understanding the genetic basis of mesothelioma hadn’t led to better diagnosis and treatments for people like my dad. I’m not the only relative of someone with a serious illness asking similar questions.

I recently told my family doctor that within three years people would be coming to him with their own genetic information. He looked puzzled and told me it would never happen. Yet this month’s UK launch of 23andMe’s Personal Genome Service means that it’s not going to take as long as three years. It’s happening now, and doctors are not ready. The repercussions are frightening.

Somehow, genomic medicine needs to do more to keep pace with progress in genomic research.

Education is the critical starting point, and that’s where I’m focusing my business right now: supporting the flow of information and raising discussion points that will help take genomics to the front lines.

REFERENCES:
(2) Green & Guyer, Charting a course for genomic medicine from base pairs to bedside. Nature, 2011: 470; 204 - 213
are genetic diseases tough to diagnose and develop treatments for. The increasing number of genomic databases should help this process significantly. But is there an ethical dilemma around allocation of time and funds towards a disease that might only affect a tiny part of the population?

With more drug developers looking into rare diseases, are we seeing a potentially dangerous shift towards prohibitively expensive treatment? Michael Vellard, has dedicated his career to curing these conditions, and is in no doubt about the social benefit of his work. He took the time to speak to us about his motivations, and how genomics is already helping drug development.

**FLG:** There are many personal stories that inspire genomic research. People see the potential benefit and the gaps they can fill, but a lot of the time it’s the experience of friends and family members with genetic diseases that drive people in the field. What is it that first got you interested in genomic research, and ultimately led you to work at Ultragenyx?

**MV:** My niece was diagnosed with Cystinosis when she was only one year old. It’s a disease that breaks up the kidneys early on in life, so that they can’t keep and absorb minerals. Kid’s with Cystinosis have to drink a lot, and are deficient in a lot of different minerals. So, often there is kidney failure early in life if they don’t get a transplant.

At the time of the diagnosis I was already studying biology, so I decided I would try work in these diseases because nothing was really known about them. Even the gene wasn’t known at the time. After I completed my PhD in Curie and Pasteur Institutes in France, I was fortunate enough to get grants to do my research wherever I wanted. So I tried to find labs that were working on Cystinosis, which led me to UCLA. The goal of my post-doctoral work there was to find and clone the gene responsible for Cystinosis. I tried that for three years, but I wasn’t successful. That was relatively hard for me, as you can imagine. From that, I took a few years of sabbatical.

After a few years out, I went back to research because I knew that I definitely wanted to do something in the field of rare genetic diseases. One of my colleagues whom I met at UCLA happened to be involved with a company that was doing exactly this; working on rare genetic diseases. The company is called BioMarin Pharmaceutical. So I ended my sabbatical, went to work at BioMarin Pharmaceutical and stayed there for 14 years. I was excited by what we were doing. It was what I wanted; to find cures for those diseases. Through those 14 years, and in the year and a half since I joined Ultragenyx, that’s pretty much what I’ve been doing.

For me, my niece was, and still is, my motivation. In my field, a lot of people are like me, with a strong personal motivation.

**FLG:** Rare diseases are a group that is often overlooked due to the relatively small market size. Value based pricing schemes have tried to make it a more lucrative prize. To what extent is there an ethical duty to research therapies for these diseases?

**MV:** There is definitely an ethical obligation, at least for me. First of all, for a lot of rare genetic diseases there is often a known treatment. So not developing this treatment because of commercial pressures, just completely blows my mind. You can develop the treatment, save kids, facilitate their lives, and to just say “no I won’t do it because I might not make money and I’m taking too much of a risk”? No. There is no doubt in my mind that I have an ethical obligation to pursue those treatments, because I know how to do it.
Morquio’s Syndrome is an autosomal recessive mucopolysaccharide storage disease. The inability to process some mucopolysaccharides can cause a variety of symptoms. Although patients with Morquio’s Syndrome may appear healthy at birth, they are likely to die at an early age. This is because of abnormal skeletal and heart development, and spinal cord compression.

The condition was first described in 1929 by both, Luis Morquio in Uruguay, and James Frederick Brailsford in England. Only 1 in 200,000 children are born with the condition today. Treatment consists of prenatal identification and enzyme replacement therapy. In February 2014, the U.S. Food and Drug Administration approved BioMarin Pharmaceutical’s drug elosulfase alfa (Vimizim) treating the disease.
Advocacy groups are also a really good place to start databases, and registries, to track the natural history of the disease. This is something that is extremely important for clinical trials. When we have natural history we know what we are going up against and we can compare the treatment against the normal evolution of the disease. These kinds of controls are extremely important to the FDA.

**FLG:** Genome databases have the potential to be extremely powerful research tools. What is the biggest benefit likely to be for drug developers?

**MV:** In the field of rare diseases, it's often very hard to correctly diagnose patients early enough. So sequencing is the first and ultimate step to confirm a diagnostic.

The relationship between the mutations that a patient might have and the pathology of the disease is also very important. From a treatment point of view, genome databases will help to adapt treatments to the patients much more effectively by knowing their specific mutations. Some mutations can give rise to relatively mild phenotypes that are very hard to diagnose. So patients that could benefit from a treatment may be ignored. Genomic databases, as they become more and more popular, should help to identify those patients.

For me, those are the two big benefits; identification of the patient and more effective treatment. Particularly if genomic sequencing helps us to identify patients as early as birth, treatments will certainly be even more effective.

**FLG:** Here in the UK the 100,000 Genomes Project is specifically looking at rare diseases as well as cancer. Even so, the nature of rare diseases is such that the relevant sample size for each rare disease is likely to be small. Do you think genome database building is going to increase dramatically over the coming years? Will integrating results from different databases significantly improve our understanding of diseases with individually small sample sizes?

**MV:** The 100,000 Genomes Project is very interesting. I think this kind of project is definitely going to become more and more popular with the price of whole genome sequencing going down so quickly. For the rare genetic diseases, it's pretty much the only way we will be able to really detect those patients. It's really a question of numbers because these are so rare. So we really need to try to sequence everyone to be able identify and to have an idea of the frequency of those specific mutations. So I think we will get more of these databases, and once we have a systematic process for sequencing the population, it will dramatically help in rare diseases.

**FLG:** How easy is it to integrate genomic information into projects already deep into development?

**MV:** We're already doing it now. In my job, for one of the diseases I'm working on, we've created a program of genotypic identification of the patient. We pay for the genotyping because we want to make sure that they have the disease we think they have, and we also really want to know which mutation they have. That really helps us adapt the treatment for those specific mutations. In rare diseases there are a lot of very different mutations with a lot of different outcomes. So at our level, that's extremely important information for us to know.
RARE DISEASES ARE ALREADY A PART OF THIS TREND TO GET MORE AND MORE INDIVIDUALISTIC, AND IT’S ALSO HAPPENING IN CANCER. BUT WILL WE HAVE THE LUXURY TO DO THIS?

**FLG:** Specifically in cases of rare diseases, keeping patient data truly anonymous can be difficult. How do you balance patient privacy with the potential benefit to research?

**MV:** A lot of people are working on how to make these databases private. TREAT-NMD, have a program where they are working on databases that ensure the patients privacy while also allowing for information to be disseminated to researchers and patients. It’s extremely difficult, but there are a lot of groups trying this. I think genomic databases are extremely important resources that scientists need open access to, but it is also very important that we protect people’s identities.

**FLG:** You recently had your own molecule approved this year. This is one that you’ve managed to develop from bench side all the way through to bedside. How does it feel to take something through that whole journey?

**MV:** The feeling is definitely an amazing feeling! Without a doubt! It was tough though. The disease I worked on was Morquio A Syndrome, which is another lysosomal disease. I started work on it about ten years ago, and it kept going back and forth. The disease itself had some challenges. Some people thought it wasn’t treatable because it has to do with bone and cartilage. Cartilage is a very hard thing to treat because it is so poorly vascularised. So a lot of people were thinking ‘let’s give up on this disease’, because it’s too hard and too risky. But I and a very small number of people didn’t! I tried to demonstrate, step-by-step, that it was possible. After a lot of ups and downs, I was lucky enough to feel the experience of being approved by the FDA and EMEA.

**FLG:** Are there any moments throughout the development and testing that really stood out as highlights for you, or people who played a pivotal role in helping you get the molecule all the way through?

**MV:** Definitely. I remember very well, early on in the process, I was visited in the lab by a young kid who had the disease. He was an extremely small guy, with all the symptoms of a Morquio A Syndrome sufferer. At one point, they used to call the disease ‘Gargoyle Disease’, so that gives you an idea of how deforming it can be. But this kid was so full of life, and so bright. In fact he went through to MIT, and is an engineer not far from here in Oakland now. The brain is completely normal, but he faces a lot of challenges. He’s in a wheelchair, has hearing difficulties, he’s around 4ft tall. He has a lot of challenges, but he’s an amazing kid. For me, this visit really drove me on. From the start, I was really pushing the research up against a lot of people who really didn’t believe in it, so I needed a lot of motivation. Meeting this patient, seeing his perspective and enthusiasm for life, was a big part of that for me. It was important for me to know that if I could do something, then I had to try to do it.

**FLG:** Is there anything you would have done differently with the benefit of hindsight?

**MV:** To panic less when I had bad results and had to fight people! I would like to have been more relaxed. But I was a passionate guy with a mission, so I pushed and carried the stress. I guess I would have liked to have been a bit more relaxed, but I don’t know if the results would have been the same though.

**FLG:** How do you think healthcare is going to change over the next 10 years?

**MV:** There are good and bad aspects to this. On the good side, I think it will become more and more individualized. Genomics will be a big part of this, enabling those kinds of personalised treatments. Rare diseases are already a part of this trend to get more and more individualistic, and it’s also happening in cancer. But will we have the luxury to do this? It costs more and more money, the more personalised a treatment is. So I don’t know if we’ll actually be able to afford those kinds of treatments. So it will most likely be a situation where we have more and more treatments, but they will also be more expensive.

**FLG:** As with the recently announced Glybera price tag?

**MV:** Yes. Although gene therapy is another issue as it is a very different business model. Obviously rare disease companies need to achieve a balance. To do this they have to, for example, make sure that pricing is not a barrier to access, providing patient support, and being thoughtful about pricing that makes rare disease drug development a viable business with the needs of the patient and the reimbursement system.

**FLG:** Congratulations again on getting your approval, and thank you for sharing your story with us. Is there anything else you’d like to say to our readers?

**MV:** For me, my story is really about following your gut and your motivations somehow. That’s what drove me.
ABOUT FRONT LINE GENOMICS EVENTS
We produce a limited number of conferences per year; two in 2015, growing to five in 2016 and seven in 2017. Our events attract between 500 and 1500 people, depending on their focus. Events consist of multiple streams (usually 6-8), each focusing on a specific topic, and typically span a period of three days. Every event includes a visionary, “TED-like”, plenary session, inspiring and shaping audience perspectives on genomics.

Each event offers opportunities for our partners to speak, exhibit, advertise, lead workshops, roundtable sessions or host specific, tailored sessions, depending on the commercial needs of your business.

EVENT SCHEDULE

Front Line Genomics events

November 3-5th 2015
San Francisco
Focus: Genome Data Analysis and Translational Genomics

June 23-25th 2015
Boston
Focus: Translational and Clinical Genomics

January 26-28th 2016
London
Focus: Translational and Clinical Genomics
WHEN OUR DOORS OPEN IN BOSTON THIS JUNE, YOU’LL KNOW THAT YOU’VE STEPPED INTO SOMETHING SPECIAL.

FOCUS:
Translational and Clinical Genomics
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EVENT OUTLINE:
Front Line Genomics ‘Boston’ will be divided into a visionary morning plenary session and 8 discrete streams occurring over the course of three days.

Join Drug Developers, Healthcare Professionals, Academics, and Patients, for an unmissable experience. Listen to inspirational talks at the Visionary Stage, hear the latest case studies, advances and methodology at 8 different zones (Genomics Medicine, Practical Clinical, Cancer, Sequencing, Data, Epigenetics, Rare Diseases, and Pharmacogenomics), get your hands on the latest technology, meet the most exciting new start-ups, and get involved. This is going to be like nothing you’ve ever experienced.

For full details visit www.frontlinegenomicsboston.com
You’ll be in good company.

HERE ARE SOME OF THE PEOPLE ALREADY HELPING TO BUILD THE GENOMICS WOODSTOCK:

- Dominique Verhelle: Director of Epigenetics, Pfizer
- Brian Dougherty: Translational Genomics Lead – Oncology, AstraZeneca R&D
- David Bick: Professor and Chief of Genetics, Medical Director of Genetics, Children’s Hospital of Wisconsin
- Georgios Stamatas: Research Associate Director and Fellow, Global SkinCare R&D, Johnson & Johnson
- Chas Bountra: Professor of Translational Medicine & Head of the Structural Genomics Consortium, Nuffield Department of Clinical Medicine
- Fahd Al-Mulla: Associate Professor, Head of Molecular Pathology, Kuwait University
- Partha Majumder: Director, NIBMG
- John McPherson: Director, Genome Technologies, Ontario Institute For Cancer Research
- David Chambers: Lecturer in Functional Genomics, Kings College London
- Lynn Dressler: Director of Personalized Medicine of the Fullerton Genetics Center, Mission Health
- Ajay Goel: Director of Epigenetics and Cancer Prevention, Baylor Research Institute, Baylor University Medical Center
- Ken Dewar: Professor, Department of Human Genetics, McGill University
- Eileen Dolan: Professor, Department of Medicine, University of Chicago
- David Von Schack: Associate Research Fellow, Clinical R&D, Precision Medicine, Pfizer
WITH GREAT POWER COMES GREAT RESPONSIBILITY

EACH ISSUE WE REVIEW A MOVIE/BOOK/TELEVISION SHOW THAT IS HELPING TO BRING GENOMICS INTO THE PUBLIC DOMAIN. IN THIS ISSUE, WE CAST OUR EYE OVER THE AMAZING SPIDER-MAN 2.

The Amazing Spider-Man 2, is our first review by virtue of being the highest profile movie featuring genomics in recent times. We did debate, starting off with GATTACA, but it’s been done to death. We wanted to take a look at what is having a major influence on how people view genomics today. The superhero movie boom is impossible to ignore at the moment, with the two houses of Marvel and DC competing on the large screen for our attention.

Long time followers of Spider-Man will be familiar with the story: a radioactive spider bites Peter Parker, a nerd, after which he develops super powers. Using the inspiration of his unfortunately deceased uncle, Peter Parker applies his talents to crime fighting.

We are now two instalments into the Marc Webb era. Webb carefully balances out the teenage drama with the superhero action to deliver a decent movie going experience. The relationship between a movie and its audience relies on a willingness to suspend disbelief. Sam Raimi’s Spider-Man trilogy asked too much of the audience. Webb, on the other hand, has tried to ground his Spider-Man universe in plausible scenarios.

This universe revolves around Oscorp. As is traditional with Hollywood, any mention of ‘corporation’ should immediately alert you to the presence of the bad guy. What do Oscorp do? Well, their Genomics department has some interesting projects! They seem to focus on genetically ‘altering’ various animals for different purposes. We have spiders that have been altered to produce incredibly strong cables; lizard DNA based gene therapies to re-grow limbs; genetically altered eels that power the city and various ‘top secret’ projects.

Predictably, things get out of hand, and a supervillain is born. In this case, Jamie Foxx, tumbles into a pool of eels and through the course of some sensational gene editing, or alarming epigenetic effects, becomes Electro, our nemesis, for the next couple of hours. We do eventually find out that the purpose of much of Oscorp’s genomics research is to find a cure for the CEO’s rare genetic disease.

For many people, this movie may well be the first time they ever hear the word ‘genomics’. What impression are they left with? The good: socially responsible projects that will transform industries. The bad: seemingly anyone who comes into contact with a genetically modified organism develops some kind of super power that drives them to destroy their city, and genetic diseases are impossible to cure. Not the greatest advertisement for the field... But the good news is that genomics is part of the zeitgeist now. That people have the wrong idea of genomics isn’t a bad thing. It’s a step up from them never having heard the term. At least these movies provide a useful conversation starter to introduce the reality of genomic research to the public!

VERDICT: OK

As pure entertainment, The Amazing Spider-Man 2 is far from the worst spend of your time. Fans of the comic book will appreciate the respect shown to the source material. Just remember it’s science fiction, not science fact.

PROS
- Spider-Man is a superhero born from genomics
- Genomics is being taken to the masses
- Andrew Garfield makes for a pretty decent Peter Parker

CONS
- No mention of real genomic research
- Not enough Paul Giamatti
- ‘Genetics’ seems interchangeable with ‘unexplainable’

RATING
6.5
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