This year, on April 16th the Personalized Medicine World Conference (PMWC) made its debut in the UK. Attendee’s benefited from new insights behind the US and UK government genome initiatives, as well as some of the personal interactions (i.e. some ‘genomic gossip’) that drove the launch of these pioneering projects. Given their high profile nature much is expected from these genome-sequencing initiatives. There were many important reflections made during the opening presentations in Oxford, by Professor’s Peter Donnelly, Eric Green and Sir John Bell, points that I believe will shape not only the lasting impact of, but also the perception of, the first era of personalised medicine.

Several of the nuggets of wisdom imparted during the opening speeches particularly caught my attention. Firstly, a point was made regarding managing public expectations and opinions. Analogy was provided through reference to European ‘public’ perception of the genetically modified crops (GMC) industry. This is a key example of how a novel technology can encounter insurmountable barriers in the face of adverse (or misplaced) perceptions. Perceptions retained for a generation or more. This immediately made me wonder, what if the current wave of initiatives over-promise what can be delivered, will ‘faith’ in personalised medicine among front-line medical staff, investors and the public result in a GMC scenario?

A second impression I took from the opening presentations of the Personalized Medicine World Conference was that there was no consistent view of what ‘personalised’ healthcare would look like or how the evidence base for creating such a personalised approach can be generated. For some, it was articulated in a manner suggesting it was a natural extension of ‘evidence based medicine’ whereby statistical association of factors mined from newly emerging ‘big data’ would refine the granularity of treatment plans or contribute to prediction of risk of future disease. For others it was more firmly related to DNA sequencing and identification of the underlying molecular defects that co-associated with an individual’s tumor; personalised diagnosis to be precise.

“Without the human genome project we would also not have microarrays, a technology that delivers highly reproducible tumor stratification and drug class response predictors.”
What’s the evidence base(s)

The outcomes of the human genome project represent a key platform for many subsequent and ongoing precision medicine efforts. For example, Foundation medicine Inc (I have no connection with this company) report that ‘three times more actionable alterations’ are detected using massively parallel DNA sequencing than traditional histopathology. Without the human genome project we would also not have microarrays, a technology that delivers highly reproducible tumor stratification and drug class response predictors using a single small sample of RNA. Thus it seems logical to extend the genome sequencing efforts to expand our knowledge of individual DNA aberrations associated with various types of cancer and other major diseases. Yet the nucleic acid that has proven to be most successful in delivering precision medicine to oncology is, beyond any doubt, RNA and not DNA.

Are we backing the wrong base in the large-scale public precision medicine initiatives, when industry is successfully turning RNA into FDA and NICE approved products? I believe so and the reasons for this are somewhat predictable. However first let’s reflect on the Foundation Medicine DNA sequencing results. In this multi cancer type analysis 1.5 events per patient were defined as being actionable. How many actionable events were restricted to a narrow class of established mutations where drug choice can be ruled in or out is unclear. Referring to data in this manner is like referring to the total number of FDA approved genomic diagnostics without referring to the fact that such tests cover an extremely narrow spectrum of usage or utility.

Could DNA analysis be utilized in the near future to offer the breast cancer patient a chemotherapy normally provided to a pancreatic cancer patient? Certainly not and this raises a point of concern regarding the need to manage expectations and the earlier point about GMC’s. To implement the first wave of precision medicine, we need solutions that are integrated (Figure 1) into current and near-future capacities not a vision of medicine in 2250.
As of today, RNA signatures are already used to develop drug-response predictors for approved drugs and those under development\textsuperscript{1,12}. And, as mentioned above, RNA signatures are used to provide prognostic information and match tumor profiles to drug response predictors. Precision medicine strategy will need to evolve in a joined-up manner, delivering ‘data’ that can be ‘interpreted’ by all phases of the patient treatment and recovery process.

In short, while discovering a subset of pancreatic cancer patients have a specific deletion in a novel kinase is valuable, in the absence of an alternative drug treatment, this information represents basic research and not something useful to the patient being profiled (Figure 2).

In contrast, a RNA signature of the patients tumor at least holds the chance of being contrasted immediately with \textit{>80} FDA approved chemotherapeutics, or those in development, and a novel option being provided today. Industrialization of this RNA approach is technically feasible and it will begin to stack the odds in the favor of finding a novel drug match to a novel tumor profile, using existing small molecule drugs or compounds.

I would also question whether more complete sequencing of an individual’s DNA, has any real potential to yield prognostics for most of the ‘common’ diseases, such as dementia or diabetes, never mind match the emerging ability of RNA diagnostics/prognostics to deliver precision medicine for Oncology. Indeed, it was very revealing that all speakers presenting DNA sequencing strategies at the PMWC, illustrated progress \textit{[sic]} of DNA approaches by presenting conventional case examples of rare childhood disease (and without doubt doing some good regarding the management of the patient). Genome wide association studies (GWAS), and more recently exome sequencing, have failed to provide diagnostic models of common chronic diseases (such dementia, diabetes or obesity) because the phenotyping in these studies is too naïve or inaccurate, or because the statistical models for analyzing DNA sequence associations remains too primitive or because the disease is largely non-genetic.

In contrast to DNA, multi-gene RNA signatures represent integrated models that combine non-linear interactions and continuous variables into genuine diagnostics that impact on patient treatment decisions, today. The real edge that RNA has over DNA, is that RNA abundance integrates genetic, epigenetic and environmental influences, capturing more variance, and so making it rather obvious why it is the nucleic acid choice for delivering precision medicine today and tomorrow, even if it is superseded some time in the future. Nevertheless, it is currently computationally intractable to explore the entire transcriptome and while data may contain a ‘diagnostic’ signature, it is not always discoverable. The same will be true for all large scale OMIC or ‘big-data’ projects.

Thus while there is no doubt in my mind that the US Precision medicine initiative and the UK \textit{100,000 Genome Project} will yield new knowledge for rare diseases and a much more refined map of the cancer genomes, I worry that this cannot be mapped sufficiently well to open up the required range of treatment options.

This brings the discussion back to managing expectations. The political backing to the recent Precision Medicine can be a double-edged
gold-standard phenotyping was unfeasible in large clinical cohorts) to identify factors that might cause disease. There have been some blindingly good successes. The association between lung cancer and smoking is so strong, that one can conclude causality. Yet the relative risk of developing lung cancer from smoking ranges from 2 up to 40-fold increase across continents reflecting differing genetics and differences in data recording methodologies. Thus if something that is so apparently causal (smoking and lung cancer) suffers from methodological challenges to see the ‘signal from noise’ then how might we gather sufficiently accurate and informative data on weaker interactions, to provide individual level assessments of risk or personalised solutions? Smart technology combined with measures of medical outcomes (or ‘health’) based on patient records is considered one promising ‘big data’ solutions to this problem. The question remains, does greater granularity (and noise) lead to better predictive models for the individual patient or simply more data and less chance to find a predictive model? (recall, exploring exhaustively multi-level interactions are beyond conventional computing).

Let’s consider the ‘health app’, which uses detection features (or battery usage) within a smart phone to track your physical movements and provide approximations of physiological traits (e.g. heart rate). Anyone that has run a clinical trial, where accelerometer and heart rate data is gathered using near clinical grade devices, will tell you that the best data are noisy. The idea that a smart phone that approximates your movements (or your 6yr old son’s movements when he takes it from you to play angry-birds) will provide a window into personalised analysis of your physical status is naïve (figure 3).

What is big data and how does it differ from traditional evidence based medicine? If you want to generate a really impressive p-value from two parameters that have a genuine interaction, then make your sample size as big as possible. This is precisely what we have seen from the Nature-published ‘mega’ GWAS studies where even the smallest of biological interactions can become ‘GWAS significant’. Population epidemiology has long relied on approximate clinical measures (because...
It is naïve for many reasons beyond the sensitivity of the parameters being measured. To personalize the relationship between physical activity and the metabolic and physiological outcomes, complex molecular phenotyping is required – simply put we all respond differently to all types of physical intervention\(^{15}\) and a given unit of physical activity, blood pressure or glucose excursion yields a ‘personal’ set of outcomes. Thus interpretation of ‘big data’ requires calibration to the individual’s biology. Current ‘big data’ gadgets replicate traditional epidemiology through the creation of data models that relate behaviors to population averages. Smarter thinking is required to make use of the data. For example, utilization of continuous data gathering technologies and ‘big data’ medical record analysis may yield numerous insights in the correct setting. Modeling links between changes in behavior and periods of ill-health may provide forewarning that an individual may benefit from taking some preventative treatment days prior to symptoms emerging (coupled with internet based surveillance data of winter flu?).

Some types of calibration might emerge from sufficient ‘big data’ modeling but whatever diagnostic emerges from modeling smart technology data, it will need to fulfill specificity and sensitivity criteria and be calibrated. These terms have still to enter the routine vocabulary of ‘big data’ – at the moment its all ‘Cloud analytics’ – referring mainly to the storage and transfer problem. In short, ‘big data’ analytics represents another potential strategy for precision medicine, but where and when it should be best deployed to improve medical diagnosis remains to be evaluated. Further, the aim is to provide personalised guidance or diagnosis, and while this can be done by studying a person over time, its unclear how n=1 treatment can be validated, when both disease and time wait for nowo(\text{man})\text{.}\) In short, we should not forget that association today is not necessarily evidence that can be used tomorrow.

**Enabling Precision Medicine**

There is no doubt in my mind that diagnosis and treatment solutions need to be advanced in parallel to avoid disappointment (Figure 4). While laboratory-based genomic technologies are advancing each year, as is our ability to capture and store ‘big data’ - our ability to model such data, or develop novel treatment strategies lags far behind. We lack computational capacity to exhaustively explore the search space of even modest ‘big data’ (e.g. a gene-chip transcriptomic profile). While the speed at which we can develop and validate molecular therapeutics remains firmly rooted in the 20th century. There are pragmatic and obvious solutions.

Firstly, greater effort should be placed on producing molecular (RNA) signatures of all chemical entities known to be safe in humans. This should include profiling all of the numerous compounds that failed (due to lack of efficacy for the original disease) in Phase II or III during the past few decades of drug developments. Such an idea is a simple extension of the connectivity database initiative\(^{46}\) but requires a broader public-private cooperation along the lines being achieved within the EU funded IMI programs and other more recent collaborative programs.

In parallel with this, a substantial investment in dramatically extending the use of transcriptome profiling in large population cohorts and intervention trials, using high-throughput chip based technologies e.g. the 384 GeneTitan platform. This not only creates novel molecular insight into disease but allows for the computational matching of poorly studied but otherwise ‘safe’ small molecular drugs (currently sitting unused in Pharmaceutical companies) and disease or phenotype response ‘figure prints’. This is a robust and emerging strategy for matching tumor characteristics with chemotherapy\(^ {6,12,17}\) and predicting which patients would benefit from treatment and what their other options might be. These are examples of RNA based precision and personalised medicine tools, while progress with metabolomics provides additional options which may transpire to be as powerful as RNA profiling.

A final comment would be that the composition of the teams leading the precision medicine initiatives must be broadened. Data gathering companies, data-logistics and gene-sequencing gurus represent an essential but narrow aspect of the experience required to meet the political expectation of Precision Medicine. We need to integrate into these teams, those experienced in drug development (clinical), along with the wealth of experience within the fields of molecular diagnostics (technical validation) and disease specialists (to help disseminate the novel approaches to colleagues). An interesting challenging is the structure of the medical profession. Clinical experts are siloed, rarely attending medical congresses out-with their clinical specialties. I recently witnessed this when attending a meeting focused on dementia, that referred to aspects of cardiovascular and metabolic disease that have long since been dismissed as overtly simplistic within those latter disciplines. As I have tried to emphasize throughout this article, the Precision Medicine revolution needs to impact, in parallel, across the entire range of activities that come together to deliver healthcare and not sequentially (pardon the pun), one phase at a time.

**Professor Timmons** has spent equal time in academic and industrial science. Following training in the physiological and pharmaceutical sciences he led lead-discovery and lead-development programs in cardiovascular and metabolic disease at Pfizer and Organon. After establishing a translational medicine project in collaboration with Karolinska Institute, Jamie moved to Sweden to oversee the completion of this muscle genomics project and then ran a group in the Centre for Genomics and Bioinformatics working with RNA based technologies. Awarded his first chair aged 35yr, he is scientific leader for an FP7 project that is developing novel ‘machine learning’ based diagnostics for ‘pre-diabetes’, as well as predictive models for cardiovascular adaptation in humans. In 2012, he set-up XRGenomics LTD which has produced the first accurate RNA diagnostic of biological ageing and he acts as a scientific advisor to companies operating in the personalised medicine arena. His unique multi-disciplinary training allows him to view the new world of Precision Medicine from multiple perspectives.
References


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