Problems, Challenges and Promises: Perspectives on Precision Medicine.

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Summary key points

•Introduction of *precision medicine*/*systems medicine* concepts and approaches

• Review of some of the challenges to the clinical implementation of *precision medicine*

• Outline of methodologies being employed to overcome these challenges

• Examination of the claims that *precision medicine* has overpromised

Author biography

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Abstract

The *precision medicine* (*systems medicine*) concept promises to achieve a shift to future healthcare systems with a more proactive and predictive approach to medicine, where the emphasis is on disease prevention rather than the treatment of symptoms. The individualisation of treatment for each patient will be at the centre of this approach, with all of a patient's medical data being computationally integrated and accessible. *Precision medicine* is being rapidly embraced by biomedical researchers, pioneering clinicians and scientific funding programmes in both the EU and USA. *Precision medicine* is a key component of both Horizon 2020 (the EU Framework Programme for Research and Innovation), and the White House's Precision Medicine Initiative. *Precision medicine* promises to revolutionise patient care and treatment decisions. However, the participants in *precision medicine* are faced with a considerable central challenge. Greater volumes of data from a wider variety of sources are being generated and analysed than ever before, yet this heterogeneous information must be integrated and incorporated into personalised predictive models, the output of which must be intelligible to non-computationally trained clinicians. Drawing primarily from the field of *oncology*, this article will introduce key concepts and challenges of *precision medicine* and some of the approaches currently being implemented to overcome these challenges. Finally, this article also covers the criticisms of *precision medicine* overpromising on its potential to transform patient care.

Article

The emergence of precision medicine

The practice of medicine is currently undergoing a paradigm shift from the primarily *reactive medicine* of the past to a more *proactive predictive medicine* aimed at disease prevention [1-9]. Rather than treating a disease, there is a shift towards the treatment of individual patients, based on a personalised data driven approach. This change is being driven by the convergence of the big data and omics revolutions. *Precision medicine* has emerged as a computational approach to functionally interpret omics and big data, and facilitate their application to healthcare provision. In this new era patients are not segregated by disease, or disease sub-type. Instead, the aim is to treat every patient as an individual case incorporating a range of personalised data including genomic, epigenetic, environmental, lifestyle and medical history. The aspiration is that the accumulation of this data into an individualised virtual representation of the patient combined with predictive modelling based on known interactions will inform rational therapy design for each patient (Fig. 1). In the words of US President Obama when he launched the Precision Medicine Initiative (PMI) on January 30th 2015, the ultimate goals and promise of *precision medicine* are "…delivering the right treatments, at the right time, every time to the right person. And for a small but growing number of patients, that future is already here…. So if we combine all these emerging technologies, if we focus them and make sure that the connections are made, then the possibility of discovering new cures, the possibility of applying medicines more efficiently and more effectively so that the success rates are higher, so that there's less waste in the system, which then means more resources to help more people -- the possibilities are boundless".

To achieve these goals *precision medicine* aims to develop computational models that integrate data and knowledge from both clinic and basic research to gain a mechanistic understanding of disease [10], thereby facilitating personalised treatment decisions. This is an extremely ambitious goal, but adopting such an approach may bring numerous rewards. For example, burgeoning healthcare costs can be reduced, and more importantly the welfare of citizens and patient outcome can be improved by systematically directing the right medicine to the right patient. We are only just embarking on this *predictive medicine* era. In these initial stages smaller disease-focused subsets of data are being profiled and used to inform clinical decisions.

Electronic health records are also pivotal to implementing the *precision medicine* revolution [11, 12]. It is envisaged that in the near future, as full clinical omic integration occurs, electronic health records will become virtual data clouds containing billions of data points on each individual patient [5]. These virtual data clouds, akin to the current cloud computing solutions (e.g. OneDrive, Google Drive, iCloud and Dropbox) would be stored remotely and accessible from any internet enabled device to authorised personnel such as the patient and their various clinicians. Electronic health records will also be used to store information gathered from longitudinal personal monitoring devices currently being developed as part of the emerging c*onnected health* sector [13-15]. As is the case with current medical records and personal data, stringent security measures would be employed to ensure the privacy of the data [8]. The requirement for computational assistance in arranging and interpreting this growing data deluge is unquestionable. Even when taking data from a single technology (genomic profiling) in a single disease class (cancer), clinicians admit that the scale of the emerging information is outpacing human cognitive capacity and that tools for interpreting the clinical significance of the data are required [16].

The complexities of the components which constitute *precision medicine* do not detract from what the implementation of *precision medicine* may mean for individual patients. The power of implementing *precision medicine* in the clinic is epitomised in the case of a patient with mosaic overgrowth with fibroadipose hyperplasia [17]. Parts of the patient's body were unaffected by the condition while other parts were massively overgrown. By sequencing and comparing the genomes of the unaffected and affected body regions of the patient, the investigators revealed a somatic mutation in the PIK3CA gene which was only present in the affected regions and was driving the overgrowth. This genomic information allowed the investigators to apply a rational therapeutic approach, and upon treatment with PI3K inhibitors the overgrown body sections normalised. In this case a personalised drug was not developed for the patient, but fortuitously the mutated gene plays a role in numerous cancers so existing therapeutics were available. This case clearly indicates how *precision medicine* approaches can be employed clinically to determine the genetic lesion driving a disease and predict the appropriate therapeutic treatment at the level of an individual patient. In addition, once this personalised approach was implemented the investigators went on to perform targeted PI3KCA sequencing in other patients with overlapping syndromes and identified mutations in the same gene in nine out of ten cases [17]. This clinical study epitomises both

the potential power and versatility of *precision medicine*, and demonstrates the clinical applicability of both global and targeted approaches.

As with any emerging area a number of variations exist for the concept of *precision medicine* (see Table 1). While some of these terms are largely interchangeable, others cover only a portion of the full concept of *precision medicine*. The terms can often represent different viewpoints on the best route ahead, or reveal the previous disciplines with which their respective proponents were affiliated. For example, the principle proponents of the *systems medicine* term tend to hail from the field of *systems biology*, whereas *genomic-era medicine* has primarily arisen from those involved with next-generation sequencing technologies. Over time the precise meaning of these terms continues to evolve from their original conception, largely as new emerging technologies and approaches are integrated, and the concepts within the field mature. It has been proposed that *precision medicine/systems medicine* is best thought of not as an academic discipline but in the terms of a conceptual framework which outlines an improved approach with which to address current and future healthcare challenges [8]. In this article *precision medicine* is used as a catchall term to encompass the current paradigm shift towards proactive *personalised medicine*. I have favoured *precision medicine* over the other terms, including that preferred by the EU Framework Programme for Research and Innovation's term *systems medicine*, as I feel it is one of the most accessible terms to a novice (be they clinician, biologist or computationalist) first coming to this field, as there is no presumption that the reader is familiar with the pre-existing field of *systems biology* (the computational and mathematical modelling of complex biological system). Furthermore, I personally feel that *precision medicine* better encapsulates the aims of this concept, its novelty and its scope. *Precision medicine* is not just *systems biology* applied to the clinic. While I appreciate the holistic aspects of the *systems medicine* term, not all *precision medicine* applications will require global profiling or multi-scale data. The *precision medicine* term has recently become preferred over *personalised medicine* to avoid implying that completely unique treatments will be designed for each individual; rather, precision medicine is more focused on classifying individuals into subpopulations with different susceptibility to a disease [18]. This article focuses on highlighting a range of *precision medicine* approaches which are showing early promise, and some of the bottlenecks to implementation which have thus far been identified. Finally, it will examine some of the contradictory claims that *precision medicine* is a revolution in health care or that it is just the latest buzz-term.

Table 1. Variations on a theme: some of the names proposed for aspects of the current healthcare revolution.

Alternative Concepts/Names	Early Usage	
Pharmacogenetics/Pharmacogenomics	*1961*	Evans, D.A.P. and Clark, C.A. *Pharmacogenetics.* British Medical Bulletin. 17: 234-240.
Systems Medicine	*1992*	Zeng B.J. *On the holographic model of human body.* 1st National Conference of Comparative Studies Traditional Chinese Medicine and West Medicine, Medicine and Philosophy.
Systems Biomedicine	*1992*	Kamada, T. *Systems biomedicine: a new paradigm in biomedical engineering.* Front Med. Biol. Eng. 4(1): 1-2.
Precision Medicine	*1997*	Wasi, P. *Human genomics: implications for health.* Southeast Asian J. Trop. Med. Public Health. 28 Suppl 2: 19-24.
Personalised Medicine	*1999*	Langreth R. & Waldholz, M. *New era of personalized medicine targeting drugs for each unique genetic profile*. The Oncologist. 4: 426-427.
Genomic-era Medicine	*2000*	Ashburn, T.T. et al. *Human tissue research in the genomic era of medicine: balancing individual and societal interests.* Arch. Intern. Med. 11-25; 160(22): 3377-84.
Predictive, Preventative, Personalized and Participatory (P4) Medicine	*2004* (initially P2 Medicine)	Hood, L. et al. *Systems biology and new technologies enable predictive and preventative medicine.* Science. 306: 640–43
Me Medicine	*2013*	Dickenson, D. *Me Medicine vs. We Medicine: Reclaiming Biotechnology for the Common Good.* Columbia University Press.
P4 Systems Medicine	*2014*	Cesario, A. et al. *P4 medicine needs P4 education.* Curr. Pharm. Des. 20(38): 6071-2.
Computational Systems Biomedicine	*2015*	Dubitzky, W. *Special issue in computational systems in biomedicine.* Briefings in Bioinformatics.

Precision medicine approaches

Precision medicine currently uses small panels of biomarkers to achieve some degree of patient stratification into disease sub-groups. However, patients are still largely stratified on a single molecular marker [19], such as the mutation status of a single gene. Single prognostic gene biomarkers that are used clinically include BRAF(V600E) in melanoma [20], MYCN in neuroblastoma [21, 22] and the BRCA genes in breast and ovarian cancer [23-25]. However, the complexity of cancer and many other human diseases requires omics-scale diagnostics to sufficiently and accurately stratify patients for personalised treatments [26]. Even when omics-scale or biomarker panels are used, treatment decisions are based on a univariate decision rule, which fails to account for interactions between the biomarkers [6],

let alone to incorporate or consider any additional factors (such as omic or environmental data) that can regulate the functioning of the biomarker panel.

Metabolomics is being exploited as an area of great potential for novel biomarker discovery, as metabolic markers represent the functional endpoint of physiological mechanisms and therefore are closely related to disease phenotype [27]. Metabolomics and the sequencing of circulating microRNAs and cell-free DNA will likely prove key to the ongoing assessment of health and disease by providing a non-invasive means of charting changes in disease states, using bodily fluids [27-30].

A move away from relying solely on static mutational data and towards dynamic omic profiling utilising technologies such as metabolomics and RNA-seq to generate functional readouts should provide enhanced disease profiling and tracking. In the near future patients will be segregated into treatment groups by not only determining their genetic mutations but also by using omic data as an output of disease network activation status. Such readouts are superior to mutational data in that they provide the functional readout of all factors affecting signalling events, such as epigenetic alterations, expression levels, copy number alterations, fusion genes, pre-post-translational modifications and environmental factors [31]. They therefore can be used to determine if the effector networks of mutated genes have indeed been altered as expected, or whether influences of genes outside of the mutation panel/genome are having compensatory influences. Utilising network-based *precision medicine* approaches will likely translate to further improving patient stratification and outcomes, as a result of fully informed clinical decision making. Computational tools already exist for predicting the activation status of signalling pathways and transcriptional regulators from omic data, such as Ingenuity Pathway Analysis (IPA) (http://www.ingenuity.com/products/ipa) [32], and they have been widely adopted by the research community. For instance, IPA has been cited in over 12,000 peer-reviewed research articles (as of October 2014). Such algorithms have improved upon advanced classical enrichment tools by also predicting the activation status (providing quantifiable levels of activation/inhibition) of enriched pathways/regulators. However, these algorithms will require improved levels of accuracy if they are to be approved for clinical use. For example, when we applied IPA to analyse differential gene expression data (RNA-seq) only, with no prior knowledge of the experiment, it could successfully identify that the cells had been treated with retinoic acid (manuscript in preparation). However, IPA only ranked retinoic acid second of all predicted upstream regulators. An additional concern with such algorithms

is that they can currently be biased towards cancer signalling, as the knowledgebase underlying them are primarily populated by data from the field of *oncology*. However as they are continually curated, their applicability to other disease types will improve as research in these diseases intensifies. A new tool that has just been launched, Qiagen Clinical Insight (June 2015), is designed specifically for clinical labs to facilitate interpreting and reporting on genomic variants identified using next-generation sequencing (http://qiagenbioinformatics.com/solutions/qiagen-clinical-insight-for-oncology). While this tool does not provide network based analysis Qiagen acquired Ingenuity Systems in 2013 and a clinical network based bioinformatics platform seems likely in the near future.

In a recent example in our own work, we globally profiled a panel of heterogeneous neuroblastoma cell lines. Neuroblastoma is a cancer which is notorious for its heterogenous outcomes and underlying genetic and epigenetic drivers, with a dearth of recurrent somatic mutations across patients [33]. Yet our network based analysis revealed that, rather than massively heterogeneous alterations in the regulators of each MYCN amplified cell line, there was a remarkable consistency in both the top regulators and their extent of activation/inhibition (under review). Perhaps, then, the real gain of *precision medicine* will be in translating the heterogeneous inputs of disease into more uniform (homogeneous) outputs which may enable the identification of common therapeutic targets which can be broadly targeted across large patient cohorts without the need for individualised drug cocktails for each patient. In the same study we found that various omic datasets (mRNA-seq, miRNA-seq, ChIP-seq and interaction proteomics) from differing platforms were best globally integrated not at the single gene level but at the level of upstream transcriptional regulators using IPA. These regulators could then be grouped into functional networks to reveal both the molecular mechanisms underlying disease states and the network vulnerabilities amenable to therapeutic targeting.

The field of *bioinformatics* (the development of methods and software tools for understanding biological data) tends to use non-mechanistic data-driven modelling approaches to make predictions. However, the field of mathematical *modelling* (the description of a system using mathematical concepts and language) primarily uses mechanistic modelling approaches to make predictions, and the application of these approaches to biological systems has largely occurred within the field of *systems biology*. *Bioinformatics* is universally considered to be an integral part of *precision medicine*. However, some *precision medicine* proponents argue that mechanistic mathematical

modelling of biological systems is also a fundamental requirement, while others do not include mechanistic mathematical modelling in their definition of *precision medicine* at all [8, 26]. The debate over the requirement of data-driven and mechanistic methodologies will ultimately be won by the practicality of which approaches achieve successful clinic implementation. In the same way that the clinical experience of heterogeneous patient response to drug treatments (which was partially responsible for the emergence of *precision medicine*), there is unlikely to be a one-size-fits-all modelling approach to address each disease. However, bioinformatic and mechanistic mathematical approaches need not be mutually exclusive and tools to support the integration and interface between both approaches will likely prove a requirement of the successful implementation of *precision medicine* [10].

Currently, there is often a subdivision of *precision medicine* into bioinformatics/statistical and mathematical/mechanistic approaches (Table 2) [8]. For a comparison of the relative strengths and weakness of each approach see 'Why model' by Wolkenhauer [34]. While such subdivision can be informative we should be cautious of fostering tribal rivalries by thinking of these approaches as mutually exclusive. While the analytical tools employed by each approach vary, a clear distinction does not necessarily exist between each approach, and their boundaries are becoming increasingly blurred. All approaches rely heavily on modern computational power and varying branches of mathematics, so a distinction between bioinformatic modelling and mathematical modelling is somewhat misleading. To overcome this blurring of boundaries it has been proposed to group approaches as being either network-based or modelling-based [8]. However this is also misleading as many modelling-based approaches are also dependent on incorporating network structure. In reality the clinical application of *precision medicine* is likely to require a fusion of approaches tailored to each individual clinical problem. For example, even if a clinical decision-assistance tool is primarily based on a mechanistic mathematical modelling approach it is likely that omics and subsequent bioinformatics analysis will be required to obtain each individual patient's parameters before they can be inputted into the mechanistic mathematical model. Just as clinicians are being required to become educated about and communicate with new disciplines so should there be an equally open flow of education and discourse between the classical disciplines of mechanistic mathematical modelling and bioinformatics.

Table 2. Some commonly used bioinformatics/statistical and mathematical/mechanistic approaches in *precision medicine*, adapted from the CASyM roadmap [8].

Approach	Discipline
Data driven modelling	*Bioinformatic*
Statistical models and regression analysis	*Bioinformatic*
Machine learning	*Bioinformatic*
Clustering and classification	*Bioinformatic*
Rule-based and logical models	*Mechanistic*
Flux and control analysis	*Mechanistic*
Dynamic deterministic methods	*Mechanistic*

Many of the bioinformatic approaches applied to *precision medicine* are currently concerned with diagnosis and treatment response prediction by molecular stratification of patients using genetic and more generally omic profiling. However, computational mathematical models are being generated to predict mode-of-action and responses-to-treatments (perturbations) not just at the molecular level but across all levels of biological organisation, including molecular, gene regulatory networks, signal transduction pathways and metabolic networks, cell populations, tissue level and whole organism models [10, 35-38]. In addition, models are being generated to account for pharmacokinetics and pharmacodynamics to analyse drug action, and even human-population level pharmacogenomics models of disease risk [10, 39, 40]. A direct challenge facing *precision medicine* is not only the generation of models at these disparate levels but the incorporation of models accounting for different levels of organisation into holistic multi-scale models [10] able to recapitulate the entire behaviour of a disease on the human system. While genetic testing may indicate a drug is safe or suitable for a patient, factors other than genetic polymorphisms have a significant effect on the results of therapy, such as epigenetic factors, patient age and gender, concomitant drug use and lifestyle factors [23]. Therefore *precision medicine* aims to integrate all of these various data types. While long established initiatives such as BioModels (http://www.ebi.ac.uk/biomodels-main/) [41-43] address model storage and open sharing needs, there is a greater challenge in *precision medicine* that remains largely unmet. This challenge is the integration of multi-modal models into a coherent framework enabling predictions of response to be made at each biological level of abstraction, both singly and simultaneously. Projects such as the Virtual Liver [44] (http://www.virtual-liver.de/), the Physiome Project (http://physiomeproject.org/) and the associated Virtual Physiological Human Institute (http://www.vph-institute.org/) are now actively tackling the issues surrounding such multi-scale model integration.

While not all treatment decisions require holistic multi-scale models, the aging demographic of the global population [45, 46] is driving increased occurrence of comorbidities. Such comorbidities result in patients being prescribed multi-drug regimens (drug cocktails), often with prescriptions coming from different healthcare specialists. In particular, various co-occurring chronic conditions can result in patients taking large quantities of medication continuously for the remainder of their lives. The implementation of multi-modal models covering numerous chronic diseases will be extremely beneficial in addressing issues of system-wide positive and negative drug synergistic effects and off-target effects for these patient cohorts. The liver provides an appropriate starting tissue for multi-modal modelling (Virtual Liver Project) for these patients, as it is the organ responsible for the ultimate processing of most medications. The prevention and control of chronic diseases has been identified as a priority by a number of global institutions, and *precision medicine* approaches are being developed to improve the outcome and quality of life of patients with such diseases, both at the disease-specific and the comorbidity level [47].

As with any ambitious initiative, a number of hurdles exist to the full implementation of *precision medicine*. The *precision medicine* community hopes to build on the previous successes of *systems biology* while simultaneously avoiding the pitfalls of interdisciplinary collaboration by implementing the lessons learned from the emergence of *systems biology* over the previous decade. Some of the challenges and bottlenecks which will have to be overcome in order to successfully implement *precision medicine* approaches in the clinic are outlined below.

Unprecedented data volumes

If anything like the envisaged patient data clouds containing billions of data points per individual [5] (covering time-resolved, omic profiling, environmental, medical and lifestyle data) is to become a reality then practical concerns relating to data heterogeneity, data storage capacity, data uniformity, consent and data protection will have to be addressed. While the cost of omic data generation continues to plummet, storage and analysis costs are not necessarily falling as rapidly, and along with data accessibility represent a major challenge to the advancement of *precision medicine*.

One means of addressing the analysis bottleneck is to train ever increasing numbers of bioinformaticians. However, the creation of graphical user interface (GUI) based tools for users without coding knowledge would not only ease the bottleneck, but also greatly lower analysis costs. This switch would be akin to the switch from text-based operating systems like MS-DOS to GUI-based operating systems such as Microsoft Windows and MAC-OS which revolutionised personal computing, making it accessible to a much wider audience and thereby increasing both the user base and functional utility of computers in everyday life. Indeed, the trend towards such GUI tools for the analysis of omics data, which minimise or remove the need for coding experience, has already begun with programmes such as Illumina's BaseSpace (https://basespace.illumina.com/home/index) and Life Technologies' Ion Reporter (https://ionreporter.lifetechnologies.com/ir/), as well as non-commercial tools such as SeqMonk (http://www.bioinformatics.babraham.ac.uk/projects/seqmonk/), Galaxy (https://usegalaxy.org/) and Helix Nebula (http://www.helix-nebula.eu/). This movement towards GUI-based analysis puts the power into the hands of a much larger user base (biological researchers, clinicians, mathematicians, etc.), rather than restricting it to pure bioinformaticians. This switch will simultaneously free many bioinformaticians from more menial repetitive analysis, allowing them to focus on refining these analytical tools and to perform more complicated analyses which will be required to advance *precision medicine*.

A move towards GUI tools for omics analysis will not in itself be sufficient to complete the objectives of *precision medicine*. Not only do user-friendly programmes for omics analysis need to be generated but modules which also interpret the data in terms of recommending personalised treatments are required. While it is feasible that this can be done by personnel with interdisciplinary expertise, the pace of novel data generation, the complexity, and the cross-talks and feedback loops being revealed in pathogenic signalling networks (particularly for multi factorial disease) makes this an increasingly difficult task more suited to integrated teams comprising a range of specialists.

There is an important unanswered question in precision medicine: at what point does data accumulation result in such diminishing returns that it stops being informative?. Inter-tumour heterogeneity could mean that every tumour within a metastatic patient would need to be profiled to predict a treatment which would be effective against all of their tumours. Worse still, the growing acknowledgement of the level of intra-tumour heterogeneity and clonal variation (blood cancers) within an individual patient [48] mean that it may not even be sufficient to profile every tumour/clone only a single time. In addition, temporal changes in

tumour/clone abundance occur, especially in response to therapeutic intervention. The advent of single cell sequencing also allows an even greater level of detail to be generated per patient or tumour. Akin to the questions about the benefits of global versus selective gene/protein/ metabolite screening, it then needs to be asked what depth of sampling detail is sufficient to make accurately predictive individualised models. If the answer to this question lies on the higher end of the scale, that would pose a further roadblock to clinical implementation of *precision medicine* as interpretive models would have to deal with an enormous amount of data, the generation of which may in itself be likely to be cost prohibitive. Therefore, will all of that additional sample data help predictions informing personalised treatments or will metastatic tumours and the combined heterogeneity within each patient mean that we should rather be looking for general combination therapeutics, on which we will have to rely anyway. If this is the case, is individualised profiling to extreme depths even necessary?

Even ignoring the issues surrounding the computational ability to handle and interpret the data deluge, a further challenge arises from this influx of new data. Correlative data, which is the primary data type being generated by patient omics and connected health initiatives, is by its very nature less reliable than functional data. Therefore, the novel findings (correlation discoveries) arising from these initiatives would ideally be subsequently functionally validated. While functional experimentation continues to improve, it still requires a much greater amount of time and labour to conduct functional studies. Therefore, it seems likely that an enormous bottleneck between the prediction of new correlations and their subsequent functional validation will arise. Similarly, there will be a long delay between the identification of novel molecular targets and the generation of new drugs directed against them.

Interpreting the data deluge at the level of the individual

The Coordinating Action Systems Medicine (CASyM) Consortium (https://www.casym.eu/) has identified a pressing need to implement methods and approaches to fill the deficit between data generation and the real impact these data are having in the clinic and community [8]. As such they have called for a *precision medicine* revolution in utilising omics-data to drive health improvements, to match the ongoing data generation revolution [8]. The development of computational models to enable researchers to map the functioning and malfunctioning of the human body, across multiple levels of structural and functional

organisation, has been identified as central to the implementation of *precision medicine* by the CASyM Consortium [8]. In addition to patient stratification for personalised treatment, *precision medicine* approaches have the potential to assist in the design of multidrug treatments and repositioning of existing drugs [39]. Mechanistic understanding of disease should facilitate the *in silico* identification of drugs approved for treatment of one condition which would be beneficial for other previously unrelated conditions, by revealing common deregulated network features and vulnerable nodes/targets. Similarly, modelling disease related signalling networks will rationalise the identification of synergistic drug combinations, by enabling the computational simulation of all conceivable drug treatment combinations across a given network [37].

While there is a diverse array of approaches being implemented to convert the data deluge (see Table 2) into actionable findings, they are all concerned with transforming complex heterogeneous data into a simple, comprehensible output. Perhaps the most common approach currently being utilised is network-based, where individualised data are incorporated into pre-constructed physiological signalling networks [35, 37]. When these networks are constructed as dynamic mechanistic models, simulations can then be performed to assess how the patient's specific data alters the output (for example, pathway activation status, transcriptional regulation or resulting phenotypes) of the network and what treatment options may return the diseased network back to a physiologically normal condition [37]. The Atlas of Cancer Signalling Network (http://acsn.curie.fr) is a free tool enabling enrichment analysis and zoom-able topographical visualisation across an extended molecular network, responsible for governing numerous areas of cancer cell behaviour. While this resource does not currently provide predictions regarding drug treatments, it is the type of large-scale integrated network tool which could be coupled to the predictive power of mechanistic models, like those described by Tortolina *et al.* [37].

The currently varied range of approaches to the visualisation of signalling networks is another challenge to wide-scale clinical implementation of network-based approaches. The adoption of standardised visualisation notation for signalling networks will aid the standardisation required for clinical implementation and enable more rapid cross model understanding and integration. It has been proposed that a shift to standardised network visualisation will provide similar benefits to the adoption of standardised notation for electrical circuits by engineers [49]. To this end, a standardised notation to define a graphical language that is unambiguous and generally understood has been suggested for generating

molecular interaction maps [49]. Once defined, the common language can be applied to any network and incorporated into pathway visualisation tools such as Pathvisio (http://www.pathvisio.org/)[50, 51].

Another major challenge facing clinical implementation is the integration of heterogeneous data types [8, 10, 52]. It is envisaged that for each patient numerous data types such as molecular, omics, high-content imaging, pathology, physiology, lifestyle and clinical will be incorporated into predictive models. While it may not be necessary to utilise all data types in every clinical scenario to obtain accurate predictive power, for example predicting response to drug treatment once a disease is diagnosed, to truly move to *proactive preventative medicine* the challenge of data integration will have to be overcome. The ultimate aim must be the automated integration (including appropriate clinical safety checks) of this heterogeneous data, if such large data volumes are to be feasibly interpreted for each individual. Despite automation being an ultimate aim, closely interacting interdisciplinary teams will initially be required for a synergistic fusion of information from disparate data types [53] to inform clinical decision making. While interdisciplinary collaborations are notoriously difficult to implement and, therefore, represent a major challenge [54], we are undoubtedly entering the era of large scale collaborative science. *Precision medicine* can avail of the experiences of previous interdisciplinary collaborations, thereby avoiding common pitfalls, such as communication barriers between disciplines and over-compartmentalisation of projects by discipline. *Precision medicine* initiatives are drawing directly from the experiences of the establishment of *systems biology* as an interdisciplinary discipline, as it is the area most closely mirroring the challenges of *precision medicine*. Indeed, *precision medicine* (*systems medicine)* is seen by many as the logical extension of *systems biology* [12], and many of the leaders of this emerging field also pioneered the advent of *systems biology* over the previous decade. However, *precision medicine* will also involve challenges which were not as prevalent in *systems biology*, such as delivering complex information to patients, integration with clinicians and healthcare systems, greater reliance on heterogeneous, static and incomplete data, conflicts between patient and industry interests and the need for modelling approaches to pass the diagnostic standards of regulatory agencies, such as the FDA.

Incorporation into the clinic

The speed at which the translation of *precision medicine* approaches are occurring means that there are cultural, technical and methodological bottlenecks which remain to be solved [53]. Education, seen as the most effective way of addressing these cultural bottlenecks, has been identified as a major challenge and priority for *precision medicine* [8, 55]. However, owing to the interdisciplinary nature of *precision medicine* and its cross-cutting of numerous medical fields, educational initiates must target a broad range of stakeholders, including clinicians, researchers, medical providers, funding agencies and patients. In addition to training in *precision medicine* for future medical personnel, current clinical practitioners and research medical doctors involved in the diagnosis and treatment of diseases will require greater familiarity with omics, data integration, modelling and bioinformatics in order to be able to incorporate them into their work. Therefore, they are being targeted by continuing medical education programmes [8]. While some *precision medicine* proponents are in favour of incorporating predictive modelling approaches into the routine diagnostic and prognostic tool kits of clinicians, others propose the creation of a new type of healthcare professional to ensure the optimal clinical (and wellness) usage of patient data clouds [3, 8, 55].

Although many clinicians contend that they have always practiced individualised and personalised medicine [19, 56], and that *precision medicine* may just represent biomedical researchers and pharmaceutical companies catching up, many clinicians aren't aware of the existence of *precision medicine*. *Precision medicine* is primarily being driven by biomedical research and industry as opposed to being a movement arising from the clinical coal face. The lack of awareness of clinicians is particularly true of those outside of fields like *oncology*, and perhaps it is correct that they have not paid much attention to these new approaches, as in many instances they have yet to deliver great clinical improvements, especially for multifactorial disease. According to one poll, as of 2012 American physicians had recommended personal genetic tests for only 4% of their patients [57]. However, efforts such as the PMI and CASyM are raising the awareness of *precision medicine* in clinical circles, and attempting to encourage clinicians to embrace this healthcare transformation. It could be fairly argued that the field of *precision medicine* is only emerging and, as discussed above, still faces many challenges, so it is unfair to expect numerous clinical success stories at this early stage. But even if it is accepted that this is the case, then the large scale funding of *precision medicine* is preceding the evidence of its applicability. Let us hope that unlike its

predecessors such as stem cell therapy, *precision medicine* can truly deliver its promised healthcare revolution.

The utility of *precision medicine* to daily clinical practice relies strongly on the availability of efficient tools to translate an individual's data into diagnosis and targeted treatments [6]. Servant and his colleagues [6] distil the requirements of such tools as data integration and traceability, safeguards to ensure correct processing and analysis and finally the application of well-defined and reproducible procedures for workflow management and decision-making. While *precision medicine* tools are currently largely in the proof-of-principle stage a future requirement will also be their usability. As has long being appreciated in the field of *bioinformatics*, it is essential that software is user-friendly [58, 59]. This is particularly true for *precision medicine* where it is expected that the user may not be computationally trained. Even in cases where analysis is performed by specialists the analysis output must be designed with user-friendly principles in mind and be interpretable to the clinicians who will base treatment decisions upon it. Research and prior examples have demonstrated that technologies which are complex are adopted more slowly [23]. To combat this, tests must not only be accurate but they must also be easy to access and use by medical staff [23]. While the output should be easily comprehensible it should not be an oversimplification. For example, it would be a waste of resources to perform whole genome sequencing only to report on the mutational status of a handful of oncogenes. Rather, models should strive to take account of the totality of data-points and distil them into a recommended course of action.

Oncology is the medical field most rapidly adopting genomic-era medicine, with most major cancer centres developing personalised medicine initiatives [6, 12, 60-65]. As such, *oncology* also appears poised to be the pioneer of *precision medicine* approaches as it seeks to interpret ever growing datasets for individual patients. *Oncology* has also been highlighted as the near-term focus of the PMI [66]. For a more complete review of current computational tools available to aid in clinical cancer decision making see Van Allen *et al.* [16]. Servant *et al.* [6] provide an excellent detailed case report on the commitment, planning and effort required and the challenges faced to successfully integrate bioinformatics based *precision medicine* into a clinical trial (the SHIVA phase II clinical trial). The SHIVA phase II clinical trial compares targeted therapy based on tumour molecular profiling with conventional therapy in patients with refractory cancer. This is an ongoing proof of principle trial for targeted therapies, and while it has thus far proved feasible [67], the outcome of this trial (results expected in 2016) and others like it will be keenly examined by the *precision medicine* community. In the

precision medicine era, clinical trials will increasingly become more stratified for, or be performed only in, molecularly well-defined patient subsets [68]. While smaller patient numbers will pose new challenges for clinical trial design [68], it is expected that determining the effectiveness of drugs will be simplified by no longer being masked by a larger cohort of non-responder participants.

The requirement for ongoing temporal profiling of patients is becoming increasingly apparent. Temporal profiling is particularly relevant in *oncology* where tumour entities rapidly evolve resistance in response to treatment and often acquire increased malignancy [69-72]. The mechanisms by which resistance arises are diverse, but include *de novo* mutations upon treatment and a treatment-mediated selection of previously minority clones. The necessity for temporal profiling of patients will greatly increase the diagnostic and computational burden of a *precision medicine* approach. However, with increased diagnostic sensitivity (e.g. increased sequencing depth) the development of *precision medicine* tools that can recommend co-treatment options to simultaneously target both majority and minority clones in a tumour could reduce the incidence of relapse and, therefore, the requirement of continued profiling.

Precision medicine should supplement and enhance current clinical tools, rather than replace them. The development of such complementary approaches has previously been suggested for integrating *precision medicine* with *pathology* [73]. Seeking to supplement existing clinical practices should also aid in the implementation of *precision medicine*, by ensuring that clinicians do not feel marginalised or criticised by practitioners from disciplines not traditionally trained to deal directly with patients. Rather, *precision medicine* should seek to empower clinicians by providing them with reliable user-friendly tools with which to convert ongoing advances in biomedical knowledge into actionable improved efficiency therapies tailored to their individual patients. Indeed, *precision medicine* seeks to go even further by empowering not only the clinicians but the patients themselves [4, 8]. This is encompassed by the participatory aspect of *P4 medicine*, where it is envisaged that decisions will be made jointly through dialogue between informed patients and their clinicians.

Precision medicine, revolution or rebranding?

The proponents of *precision medicine* hail it as a health care revolution, while its detractors think that it is merely rebranding the claims originally attributed to the sequencing of the

human genome for a new decade. Although the term *precision medicine* has been around for a long time (Table 1) it has only very recently emerged as a dominant name for this field, being a conscience rebranding of the *personalised medicine* term by US health agencies and the current White House administration, to give *personalised medicine* a fresh start and essentially resetting the clock [74].

The President of the U.S. highlighted the hope of new medical breakthroughs, stating firstly that "This landmark achievement will lead to a new era of molecular medicine, an era that will bring new ways to prevent, diagnose and treat disease", and secondly "..precision medicine gives us one of the greatest opportunities for new medical breakthroughs that we have ever seen…. the possibilities are boundless". However, the first statement is from President Clinton announcing the draft of the Human Genome Project (June 26th 2000), while the second is from President Obama (January 30th 2015) fifteen years later announcing the Precision Medicine Initiative (PMI). Clearly the claims and hope for medical advancement arising from the Human Genome Project and the PMI are very similar. *Precision medicine* is in many ways a direct descendant of the Human Genome project [75] so it is logical that they both share similar aspirations. However the need for the PMI is also testament to the fact that the sequencing of the human genome has thus far failed to live up to all the initial claims of the degree of medical advancement it would achieve. This failure is understandable in light of the continued discovery of increasingly complex levels of biological organisation. Genome sequencing has of course progressed medical science; but the rate of progression has been far from uniform with the greatest advances being observed in disease with a single genetic cause. It is in this light that one must reflect on the claims of *precision medicine* and wonder whether in another fifteen years, or less, a new US President will be making similar claims about a new 'revolution' in health care aimed at addressing all of the multifactorial diseases that *precision medicine* approaches failed to improve more than incrementally. To give President Obama credit, the lessons about the claims of previous 'revolutions' have not gone unheeded and he is more realistic about the timeframe of these new advances, stating that "medical breakthroughs take time, and this area of precision medicine will be no different".

It is possible that like a number of 'revolutions' before it the *precision medicine* revolution will not lead to the fulfilment of its claims, but rather incremental gains on a case by case basis. Another such example is the stem cell 'revolution' which has not yet materialised and has fallen out of favour, but continues to make incremental gains. The *precision medicine* fervour maybe more of a reflection of it being the buzz-word of the current research funding

cycle, and the hope of industrial financial interests than from myriad examples of concrete clinical improvements with lasting patient benefit. Targeted therapies such as the use of BRAF(V600) inhibitors in malignant melanoma can often achieve dramatic clinical improvements but these are often short lived as tumours quickly adapt, evolving resistance to the drug [20]. Thus far the majority of successes have been in single gene disorders [19], and, just as with earlier attempts, multi-gene and indeed multifactorial diseases are not being overcome as easily by *precision medicine* approaches.

Detractors of *precision medicine* contend that its realisation would involve unrealistic costs, and that much of the cost associated with continual screening programmes would need to be pushed from public and private health care to individuals [75], for example by encouraging private individuals to pay for the sequencing their genome. With ongoing debates existing over the benefits and costs of population based screening programmes (such as mammography screening for breast cancer [76, 77]) which are relatively cheaper, financially and analytically, than many proposed *precision medicine* programmes, the sustainability of the funding of on-going genomic-era population screening really comes into doubt. While the cost of genome sequencing is falling, data storage and analysis costs are still high. This becomes particularly important when you consider diseases as dynamic rather than static entities. Sequencing a person's genome once (at birth or diagnosis) may provide risk stratification and diagnostic functions (having the original sequence to compare with later ones would also be an advantage) but would provide no information about the state the individual's disease state later on. Any subsequent disease or change in a disease due to somatic mutations or environmental factors (e.g. viral, contaminant exposure) would require additional rounds of sequencing. An additional current cost of the massive investment in *precision medicine* is that it is diverting funding from other more traditional and proven treatments and research which, although not without their faults, previous medical advances have been based on [75].

While holding great promise for the improvement of healthcare provision and wellness, the realisation of *precision medicine* approaches will bring with it genuine ethical and social concerns [78], as well as new regulatory challenges [79], all of which will have to be considered. Not least of these is the issue surrounding ownership of bio-banked samples and individual genomes, which currently are the property of the public institutions and private corporations which house samples and data [75]. Potential also exists for the misuse of *precision medicine* to further pave the way for the commercialisation of health (as opposed to

disease) by feeding on individual's fears (risk factors, predisposition etc.), to sell preventative medication which must be taken continually throughout their life, before having even contracted a disease, with massive financial implications. Disputes will also likely arise about whether precision treatments should be pharmaceutically or lifestyle based. One need only look at the epidemic scale increase in the diagnosis of attention deficit hyperactivity disorder (ADHD) and the concomitant increase in the use of prescription drugs [80-82]. While the symptoms ADHD may be better prevented by a cultural change, re-assessing the demands placed on children and providing an educational environment more in tune with children's innate learning abilities [83], the corporate interests of pharmaceutical companies appear to be winning out as drug sales soar [82]. *Precision medicine* will likely create further situations where the interests of patients, clinicians, insurance companies, government agencies, and the pharmaceutical industry do not fully coincide [19].

Another concern surround some of the grander claims of *precision medicine* proponents is whether the combination of biological and environmental complexity will prove too great to be globally overcome by modelling in the near future. More data does not necessarily translate into more knowledge; rather it can mean an increase in noise. Targeted panels may be more practical and informative than global multi-scale investigation for every individual. There are very few examples outside of tightly controlled model systems where genuine multi-scale data integration has been achieved. Is it realistic to think that even those models that can perform well in tightly controlled and standardised biological model systems when transferred to heterogeneous populations with even more heterogeneous environmental interactions will maintain their predictive power?

Beyond the hype of *precision medicine*, the provision of healthcare advice has largely been notoriously unsuccessful at halting epidemics such as obesity, and it remains to be seen whether personalising the advice will garner tangible improvements on past outcomes. With the generation of the personal health data clouds of *precision medicine* and the continuous monitoring of *connected health* we should be wary of instilling the belief in the general public that life is a disease waiting to happen. To this end, disease marker data should only ever be prominent and highlighted to an individual upon reaching a certain detection limit, and even then it should be communicated to the patient only by a healthcare professional. Such precautions do not limit the utility of *connected health* tools for the tracking of healthy lifestyle approaches; it merely keeps the focus of their human interaction on health rather than disease.

Despite these concerns, *precision medicine* promises to revolutionise healthcare provision. The question is not whether this revolution can fulfil its promises, but rather how many and what specific areas of health will benefit from this new approach. In summary, while the ambitions of *precision medicine* are extremely laudable, and will transform myriad facets of medical care, it will require a concerted community effort to overcome the existing obstacles to fully implement *precision medicine* in healthcare provision.

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References

1. Zhang Z, Zhao Z, Liu B et al. Systems biomedicine: It's your turn—Recent progress in systems biomedicine, Quantitative Biology 2013;1:140-155.
2. Vandamme D, Fitzmaurice W, Kholodenko B et al. Systems medicine: helping us understand the complexity of disease, QJM 2013;106:891-895.
3. Hood L, Auffray C. Participatory medicine: a driving force for revolutionizing healthcare, Genome Medicine 2013;5:110.
4. Hood L, Friend SH. Predictive, personalized, preventive, participatory (P4) cancer medicine, Nat Rev Clin Oncol 2011;8:184-187.
5. Hood L, Balling R, Auffray C. Revolutionizing medicine in the 21st century through systems approaches, Biotechnology Journal 2012;7:992-1001.
6. Servant N, Roméjon J, Gestraud P et al. Bioinformatics for Precision Medicine in Oncology: principles and application to the SHIVA clinical trial, Frontiers in Genetics 2014;5.
7. Sobradillo P, Pozo F, Agustí Á. P4 Medicine: the Future Around the Corner, Archivos de Bronconeumología ((English Edition)) 2011;47:35-40.
8. Consortium TC. The CASyM roadmap: Implementation of Systems Medicine across Europe, version 1.0. 2014.
9. Flores M, Glusman G, Brogaard K et al. P4 medicine: how systems medicine will transform the healthcare sector and society, Personalized medicine 2013;10:565-576.
10. Wolkenhauer O, Auffray C, Brass O et al. Enabling multiscale modeling in systems medicine, Genome Medicine 2014;6:21.

11. Pathak J, Kho AN, Denny JC. Electronic health records-driven phenotyping: challenges, recent advances, and perspectives, Journal of the American Medical Informatics Association 2013;20:e206-e211.
12. Cesario A, Auffray C, Agusti A et al. A Systems Medicine Clinical Platform for Understanding and Managing Non- Communicable Diseases, Current Pharmaceutical Design 2014;20:5945-5956.
13. Ranck J. Connected Health: How Mobile Phones, Cloud and Big Data Will Reinvent Healthcare San Francisco, CA: GigaOM Books, 2012.
14. Bogan D, Spence J, Donnelly P. Connected Health in Ireland: An All Island Review. 2010.
15. Health Do, Executive HS, First PS. eHealth Stragety for Ireland. http://health.gov.ie/blog/publications/ehealth-strategy-for-ireland/.
16. Van Allen EM, Wagle N, Levy MA. Clinical Analysis and Interpretation of Cancer Genome Data, Journal of Clinical Oncology 2013;31:1825-1833.
17. Lindhurst MJ, Parker VER, Payne F et al. Mosaic overgrowth with fibroadipose hyperplasia is caused by somatic activating mutations in PIK3CA, Nat Genet 2012;44:928-933.
18. Disease CoAFfDaNTo. Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease. Washington, DC: National Research Council of the National Academies, 2011.
19. Jameson JL, Longo DL. Precision Medicine — Personalized, Problematic, and Promising, New England Journal of Medicine 2015;372:2229-2234.
20. Luke JJ, Hodi FS. Ipilimumab, Vemurafenib, Dabrafenib, and Trametinib: Synergistic Competitors in the Clinical Management of BRAF Mutant Malignant Melanoma, The Oncologist 2013;18:717-725.
21. Cohn SL, Pearson ADJ, London WB et al. The International Neuroblastoma Risk Group (INRG) Classification System: An INRG Task Force Report, Journal of Clinical Oncology 2009;27:289-297.
22. Huang M, Weiss WA. Neuroblastoma and MYCN, Cold Spring Harbor Perspectives in Medicine 2013;3.
23. Hess GP, Fonseca E, Scott R et al. Pharmacogenomic and pharmacogenetic-guided therapy as a tool in precision medicine: current state and factors impacting acceptance by stakeholders, Genetics Research 2015;97:null-null.
24. Miki Y, Swensen J, Shattuck-Eidens D et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1, Science 1994;266:66-71.
25. Wooster R, Bignell G, Lancaster J et al. Identification of the breast cancer susceptibility gene BRCA2, Nature 1995;378:789-792.
26. Zhang H, Gustafsson M, Nestor C et al. Targeted omics and systems medicine: personalising care, The Lancet Respiratory Medicine 2014;2:785-787.
27. Eckhart AD, Beebe K, Milburn M. Metabolomics as a Key Integrator for “Omic” Advancement of Personalized Medicine and Future Therapies, Clinical and Translational Science 2012;5:285-288.
28. Sun J, Beger RD, Schnackenberg LK. Metabolomics as a tool for personalizing medicine: 2012 update, Personalized medicine 2013;10:149-161.
29. Inns J, James V. Circulating microRNAs for the prediction of metastasis in breast cancer patients diagnosed with early stage disease, The Breast 2015.
30. Tiberio P, Callari M, Angeloni V et al. Challenges in Using Circulating miRNAs as Cancer Biomarkers, BioMed Research International 2015;2015:10.
31. Greenblatt SM, Nimer SD. Chromatin modifiers and the promise of epigenetic therapy in acute leukemia, Leukemia 2014;28:1396-1406.
32. Krämer A, Green J, Pollard J et al. Causal analysis approaches in Ingenuity Pathway Analysis, Bioinformatics 2014;30:523-530.
33. Pugh TJ, Morozova O, Attiyeh EF et al. The genetic landscape of high-risk neuroblastoma, Nat Genet 2013;45:279-284.
34. Wolkenhauer O. Why Model?, Frontiers in Physiology 2014;5.

35. Gustafsson M, Nestor C, Zhang H et al. Modules, networks and systems medicine for understanding disease and aiding diagnosis, Genome Medicine 2014;6:82.
36. Meinhardt H. Modeling pattern formation in hydra: a route to understanding essential steps in development, Int. J. Dev. Biol. 2012;56:447-462.
37. Tortolina L, Duffy DJ, Maffei M et al. Advances in dynamic modeling of colorectal cancer signaling-network regions, a path toward targeted therapies, Oncotarget 2015;6:5041-5058.
38. Kholodenko BN, Hancock JF, Kolch W. Signalling ballet in space and time, Nat Rev Mol Cell Biol 2010;11:414-426.
39. Vandamme D, Minke BA, Fitzmaurice W et al. Systems biology-embedded target validation: improving efficacy in drug discovery, Wiley Interdisciplinary Reviews: Systems Biology and Medicine 2014;6:1-11.
40. Swat M, Kiełbasa SM, Polak S et al. What it takes to understand and cure a living system: computational systems biology and a systems biology-driven pharmacokinetics–pharmacodynamics platform, Interface Focus 2010;1:16-23.
41. Le Novère N, Bornstein B, Broicher A et al. BioModels Database: a free, centralized database of curated, published, quantitative kinetic models of biochemical and cellular systems, Nucleic Acids Research 2006;34:D689-D691.
42. Chelliah V, Juty N, Ajmera I et al. BioModels: ten-year anniversary, Nucleic Acids Research 2014.
43. Li C, Courtot M, Le Novère N et al. BioModels.net Web Services, a free and integrated toolkit for computational modelling software, Briefings in Bioinformatics 2010;11:270-277.
44. Drasdo D, Hoehme S, Hengstler JG. How predictive quantitative modelling of tissue organisation can inform liver disease pathogenesis, Journal of Hepatology 2014;61:951-956.
45. Lutz W, Sanderson W, Scherbov S. The coming acceleration of global population ageing, Nature 2008;451:716-719.
46. Division UNDoEaSAP. World Population Ageing: 1950-2050. United Nations. New York: United Nations, 2002.
47. Bousquet J, Jorgensen C, Dauzat M et al. Systems Medicine Approaches for the Definition of Complex Phenotypes in Chronic Diseases and Ageing. From Concept to Implementation and Policies, Current Pharmaceutical Design 2014;20.
48. Burrell RA, McGranahan N, Bartek J et al. The causes and consequences of genetic heterogeneity in cancer evolution, Nature 2013;501:338-345.
49. Kohn KW, Aladjem MI, Kim S et al. Depicting combinatorial complexity with the molecular interaction map notation. 2006.
50. Luna A, Sunshine ML, van Iersel MP et al. PathVisio-MIM: PathVisio plugin for creating and editing Molecular Interaction Maps (MIMs), Bioinformatics 2011;27:2165-2166.
51. Kutmon M, van Iersel MP, Bohler A et al. PathVisio 3: An Extendable Pathway Analysis Toolbox, PLoS Comput Biol 2015;11:e1004085.
52. Dubitzky W, Krebs O, Eils R. Minding, OLAPing, and Mining Biological Data: Towards a Data Warehousing Concept in Biology, NETTAB - Network Tools and Applications in Biology 2001.
53. Capobianco E, Lio' P. Advances in Translational Biomedicine from Systems Approaches, Frontiers in Genetics 2014;5.
54. Wolkenhauer O, Auffray C, Jaster R et al. The road from systems biology to systems medicine, Pediatr Res 2013;73:502-507.
55. Cesario A, Auffray C, Russo P et al. P4 Medicine Needs P4 Education, Current Pharmaceutical Design 2014;20.
56. Gibson WM. Can Personalized Medicine Survive?, Canadian Family Physician 1971;17:29-88.
57. Modernization. UHCfHRa. Personalized Medicine: Trends and Prospects for the New Science of Genetic Testing and Molecular Diagnostics.
http://www.unitedhealthgroup.com/~/media/UHG/PDF/2012/UNH-Working-Paper-7.ashx, 2012.

58. Javahery H, Seffah A, Radhakrishnan T. Beyond power: making bioinformatics tools user-centered, Commun. ACM 2004;47:58-63.
59. Brooksbank C, Bergman MT, Apweiler R et al. The European Bioinformatics Institute's data resources 2014, Nucleic Acids Research 2014;42:D18-25.
60. Fenstermacher DA, Wenham RM, Rollison DE et al. Implementing Personalized Medicine in a Cancer Center, Cancer journal (Sudbury, Mass.) 2011;17:528-536.
61. Garraway LA, Verweij J, Ballman KV. Precision Oncology: An Overview, Journal of Clinical Oncology 2013;31:1803-1805.
62. Meric-Bernstam F, Farhangfar C, Mendelsohn J et al. Building a Personalized Medicine Infrastructure at a Major Cancer Center, Journal of Clinical Oncology 2013;31:1849-1857.
63. Mendelsohn J. Personalizing Oncology: Perspectives and Prospects, Journal of Clinical Oncology 2013;31:1904-1911.
64. Schilsky RL. Implementing personalized cancer care, Nat Rev Clin Oncol 2014;11:432-438.
65. Madhavan S, Gusev Y, Harris MA et al. G-CODE: enabling systems medicine through innovative informatics, Genome Biology 2011;12:P38-P38.
66. Collins FS, Varmus H. A New Initiative on Precision Medicine, New England Journal of Medicine 2015;372:793-795.
67. Le Tourneau C, Paoletti X, Servant N et al. Randomised proof-of-concept phase II trial comparing targeted therapy based on tumour molecular profiling vs conventional therapy in patients with refractory cancer: results of the feasibility part of the SHIVA trial, Br J Cancer 2014;111:17-24.
68. Sleijfer S, Bogaerts J, Siu LL. Designing Transformative Clinical Trials in the Cancer Genome Era, Journal of Clinical Oncology 2013;31:1834-1841.
69. Bedard PL, Hansen AR, Ratain MJ et al. Tumour heterogeneity in the clinic, Nature 2013;501:355-364.
70. Fisher R, Pusztai L, Swanton C. Cancer heterogeneity: implications for targeted therapeutics, Br J Cancer 2013;108:479-485.
71. Kuster L, Grausenburger R, Fuka G et al. ETV6/RUNX1-positive relapses evolve from an ancestral clone and frequently acquire deletions of genes implicated in glucocorticoid signaling. 2011.
72. Morak M, Attarbaschi A, Fischer S et al. Small sizes and indolent evolutionary dynamics challenge the potential role of P2RY8-CRLF2–harboring clones as main relapse-driving force in childhood ALL. 2012.
73. Caie PD, Schuur K, Oniscu A et al. Human tissue in systems medicine, FEBS Journal 2013;280:5949-5956.
74. Timmerman L. What's in a Name? A Lot, When It Comes to 'Precision Medicine'. Xconomy. http://www.xconomy.com/national/2013/02/04/whats-in-a-name-a-lot-when-it-comes-to-precision-medicine/: Xconomy, 2013.
75. Dickenson D. Me Medicine vs. We Medicine: Reclaiming Biotechnology for the Common Good. New York: Columbia University Press, 2013.
76. McPherson K. Screening for breast cancer—balancing the debate. 2010.
77. Barratt A. Overdiagnosis in mammography screening: a 45 year journey from shadowy idea to acknowledged reality. 2015.
78. Juengst ET, Settersten RA, Fishman JR et al. After the revolution? Ethical and social challenges in 'personalized genomic medicine', Personalized medicine 2012;9:429-439.
79. Evans BJ, Burke W, Jarvik GP. The FDA and Genomic Tests — Getting Regulation Right, New England Journal of Medicine 2015;372:2258-2264.
80. Lardizabal A. Is Financial Gain to Blame for the Growing ADHD Epidemic?, Journal of Child and Adolescent Psychiatric Nursing 2012;25:164-164.
81. Conrad P, Bergey MR. The impending globalization of ADHD: Notes on the expansion and growth of a medicalized disorder, Social Science & Medicine 2014;122:31-43.

82. Sharpe K. Medication: The smart-pill oversell, Nature 2014;506:146-148.
83. Gray P. Free to Learn: Why Unleashing the Instinct to Play Will Make Our Children Happier, More Self-Reliant, and Better Students for Life. New York: Basic Books, 2013.

Figure Legends

Figure 1. An overview of the *precision medicine* approach. The figure visualises the order and complex interconnections of the numerous interacting components which, when incorporated, give rise to *precision medicine*.

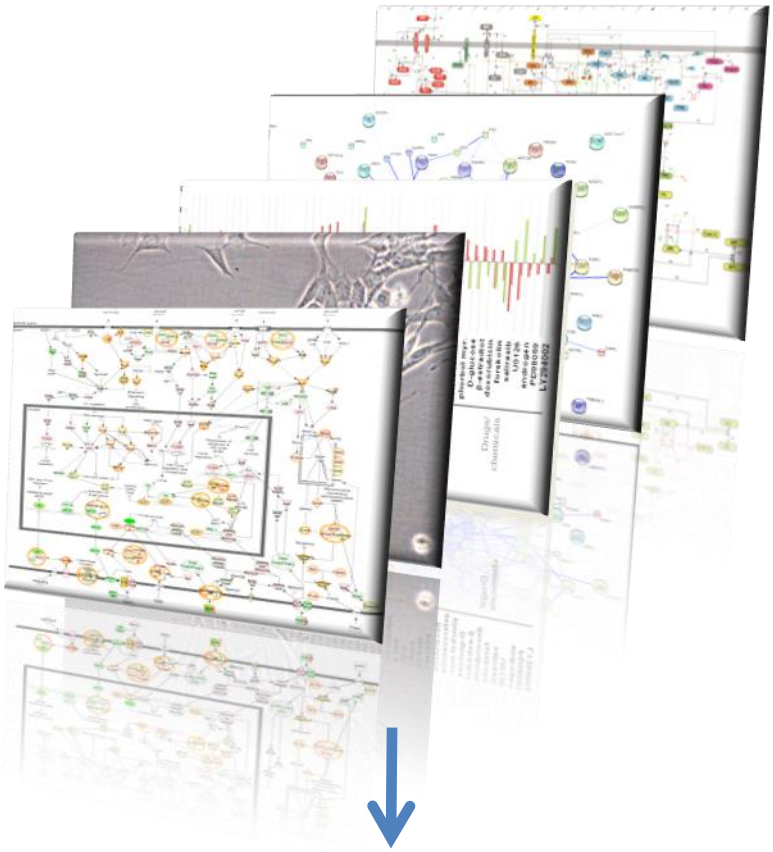
Systems Medicine Overview

Data Generation

medical history | omics | environ-ment | connected health

Individualised Patient Data Cloud

Predictive Modelling



Follow-up & Continuous Monitoring

Basic & Applied Research

Personalised Therapy & Lifestyle Recommendations