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What do leaders of disease-specific advocacy organizations know about pharmacogenomics and biomarkers, anyway?

Disease Advocacy Organizations (DAOs) make meaningful contributions to the development of tests and therapeutics across the development pipeline, from cohort development to actual drug discovery. The process of developing biomarkers and validating them is fraught with a high failure rate and enormous expense. DAOs can harness new information technologies to increase effectiveness, including systems to dynamically consent individuals to participate in registries and trials. These new technologies can alleviate some of the expense in biomarker development. Information aggregation with consumer control of information at its core will eventually permit a national surveillance system for pre- and post-treatment analysis. A stronger and more scientific basis on which to build quality control and assurance of biomarker determination is needed. Validation must be supported in the future, in the same manner discovery was in the past, including through federal funding and philanthropic giving. DAOs can accelerate the process of biomarker development by building robust, well-characterized cohorts.

KEYWORDS: advocates ■ biomarkers ■ clinical trials ■ consumers ■ drug development ■ networks ■ therapy

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The future is a world where we understand the pathomechanisms of disease, use precise biomarkers to measure the efficacy of a multitude of safe and effective treatments in order to tailor them to the individual in a specific environment, and monitor all events, adverse and otherwise, through ubiquitous and easily accessible surveillance systems that ensure person-centered and specific privacy and confidentiality controls. Of course, all of this is paid for by a comprehensive health and wellness care system. We are not so naive as to believe this scenario will be realized any time soon, but we do think this future is achievable. We are not even too troubled when we do not understand the disease pathway. We are certainly satisfied with safe and effective treatments, even if we do not understand their mechanism of action. To accelerate the discovery of tests and therapeutics, Disease Advocacy Organizations (DAOs) are engaged in all aspects of therapeutic development and in some cases are leading the way, for example, in Marfan syndrome [1] and cystic fibrosis [2]. We understand the enormous complexity of the major scientific hurdles in both common and rare diseases. Nevertheless, the greatest impact DAOs appear to be ready to make is in the realm of cohort development, while exploring new models and systems to encourage and aid translational science.

At the core of personalized, or individualized, medicine is the translation of genetic and/or genomic information to relevant personal health information. This translation requires that tests and therapies be measured against appropriate clinical end points. These clinical end points are not easy to determine and quantify, and their validation, and that of companion drug targets, is a complex and difficult process. Though basic research has thrived in the last few decades, these steps in the therapeutic pipeline have not been so successful (Figure 1). A recent US Government Accounting Office report stated:

> *"On average, drug sponsors can spend over 13 years studying the benefits and risks of a new compound, and several hundred millions of dollars completing these studies before seeking US FDA's approval. Approximately one out of every 10,000 chemical compounds initially tested for their potential as new medicines is found to be safe and effective and eventually approved by the FDA, making the drug discovery and development process complex, time consuming, and costly"* [3].

The drug development industry is being further challenged as personalized medicine begins to shift success away from blockbuster drugs and towards drugs for stratified populations with no obvious pathway to profit. This stratification requires accurate assays. At the same time, many DAOs have transformed themselves to facilitate test and therapeutic development leading to health outcomes.

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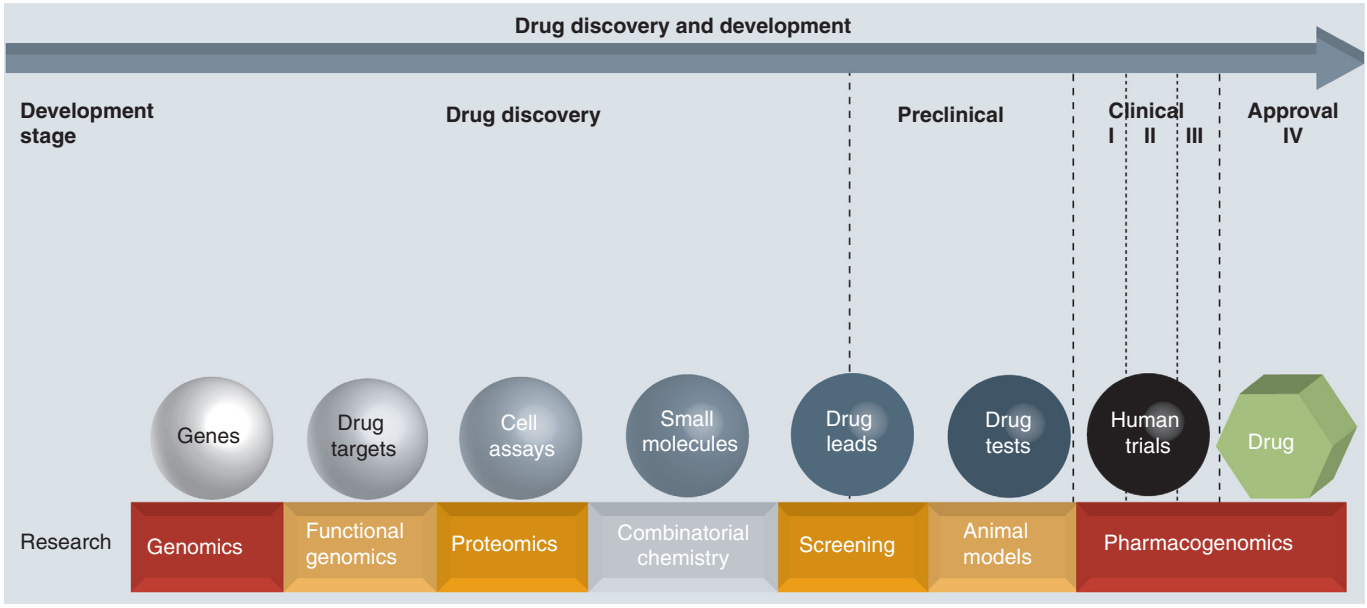

Figure 1. Drug discovery and development. The drug development pipeline. Currently only genes are in the 'information commons'.

DAOs are typically nonprofit (charity) organizations dedicated to the support of individuals affected by a specific condition and/or researching the disease for the expressed purpose of discovering therapies. There are thousands of these groups worldwide. They have been most active in the USA, although most US DAOs have an international reach. DAOs have become interested in and vocal with regard to pharmacogenomics and biomarkers in recent years. This follows their increasing participation in, and even management of, research and policy on specific diseases [4–6]. The DAOs' lay and scientific leadership for many diseases – including breast, ovarian, pancreatic and colorectal cancers – have written journal articles, white papers and position statements, and offered testimony on science and policy issues associated with biomarkers [7,101–103]. In addition, organizations dedicated to both rare and common conditions are expending resources in elucidating biomarkers for their associated conditions, sometimes simply by funding the work, and other times engaging in the research themselves [8,9,104,105]. These organizations are eager for the billions of dollars dedicated to biomedical research, both in the public and private sector, that can lead to disease-free survival with a high quality of life. Some are very impatient and demanding, and others are working iteratively. None are satisfied with the *status quo*.

First-hand experience of disease advocacy organizations' efforts

With my husband, I am the cofounder of a DAO for the rare condition pseudoxanthoma elasticum (PXE). In addition, and more pertinent to this perspective piece, I am also the President and Chief Executive Officer of Genetic Alliance (DC, USA). In 1986, Genetic Alliance began as a membership organization of hundreds of DAOs specific to genetic conditions, even prior to the Human Genome Project's inception [106]. Concurrent with the dramatic advances in genetics, including the rise of molecular diagnostics and genome-wide association studies for common conditions, Genetic Alliance expanded its network and mission, and now includes more than 10,000 organizations from all stakeholder groups working in genetics and genomics. This network is international, since a key tenet of Genetic Alliance is openness, creating boundaryless systems to share methods, resources, results and products. Its mission is to transform health through genetics. It promotes an environment of openness to improve the health of individuals, families and communities. Genetic Alliance convenes diverse stakeholders – including disease-specific advocacy organizations, universities, companies, government agencies and policy organizations – to explore and create novel partnerships in advocacy. Its network provides an open space for shared resources, creative tools and dozens of timely programs. Genetic Alliance identifies solutions to emerging problems and reduces obstacles to the rapid and effective translation of research into accessible technologies and services that improve human health. In all Genetic Alliance does, it integrates individual, family and community perspectives to improve health systems. Genetic Alliance revolutionizes access to information to enable the translation

of research into services and individualized decision making. Genetic Alliance offers technical assistance to organizations, builds and sustains robust information systems, and actively works for public policies that promote the advancement of healthcare for the common good.

My perspective on personalized medicine and biomarkers is very much influenced by the stakeholder group to which I belong. I am the parent of two children with PXE. PXE is a recessively inherited genetic condition, caused by mutations in the ATP-binding cassette subfamily C member 6 (*ABCC6*) gene. The mechanism of action is not known, but my husband Pat Terry and I do know that mutations in this gene cause mineralization of the mid-dermis, Bruch's membrane and the midlaminar layer of midsized arteries. This mineralization leads to lax and redundant skin in the flexor areas, neovascularization that leads to central vision loss and various cardiovascular problems [10]. Our children were diagnosed in late 1994, and in early 1995 my husband and I founded PXE International (DC, USA). From the start, we were committed to creating a system that would lead to the development of a therapeutic for this condition, and created PXE International to focus on that mission. Though neither my husband nor I had any science background, we quickly understood that there was no roadmap for characterizing a disease, building cohorts for clinical trials, establishing appropriate biomarkers, developing assays and testing a therapeutic [11].

My husband and I put together a plan from our 'citizen scientist' perspective [12], which we followed in the absence of any other map (Figure 2). We met with scientists, built a biobank, created a registry of thousands of affected individuals, collected clinical information from them, engaged in wet bench work, discovered the gene, patented the gene, turned over the rights to PXE International, participated in a federal program called Collaboration, Education, and Test Translation [13] to develop a genetic test, licensed the test to a company that is part of a rare disease laboratory network, and have begun the quest for a therapy. Throughout this we have partnered with dozens of scientists from academia, government and companies.

Network solutions

Over the course of this work, it became quite clear that the issues my husband and I faced were common to all diseases. It was also clear that some of the issues were either exacerbated or simplified by the rarity of the disease. For example, the lack of scientific interest in PXE is a typical casualty of the orphan nature of the condition – it is estimated to affect only one in 50,000 people. Because the number of patients, treating clinicians and researchers is limited, it is relatively easy to build a networked community that is committed to finding solutions and sharing information, biological samples and resources [6]. This sometimes creates a much simpler system than those dedicated to more common conditions. On the other hand, more common conditions, such as Type 1 diabetes [14,15] and muscular dystrophy [16], have created clinical research networks that have far more resources and a greater reach than those used in rare diseases. However, there is a convergence of the two ends of the disease prevalence continuum, as it now seems likely that most common diseases have common variants of weak effect and rare variants of large effect. These rare mutations probably contribute to common diseases [17], thus work on rare diseases will have benefits for common diseases. Particularly as biomarkers are developed, it will be critical to properly stratify populations, in effect, using genetic and genomic tests to break common diseases into rare subsets, so that proper therapeutic response, and perhaps disease progression, can be discerned. Furthermore, it is clear that organ systems may not matter as much as disease pathways in biomedical research, and working on the science with systematic, comprehensive methods focused on health outcomes appears to be much more effective than siloing a single disease and attempting to create all of the infrastructure necessary to do genetic studies, characterize the phenotype and progression, and develop meaningful clinical end points. PXE provides a good illustration of this. The clinical phenotype is a result of the mineralization of selected elastic fibers. It was therefore thought that the gene associated with PXE would be implicated in connective tissue structure. In fact, the gene is a member of the ATP-binding cassette subfamily C, like *CFTR*, and is responsible for a metabolic function [18], perhaps of vitamin K in the liver [19,20]. It appeared that working in collaboration with other diseases would create the fastest track to advances in PXE.

For all these reasons, my husband and I combined our efforts with others under the umbrella of Genetic Alliance. Assuming the leadership of this organization was a daunting but exciting task. The challenges of capitalizing on the abundant information coming from the Human Genome Project were emerging as fast as the

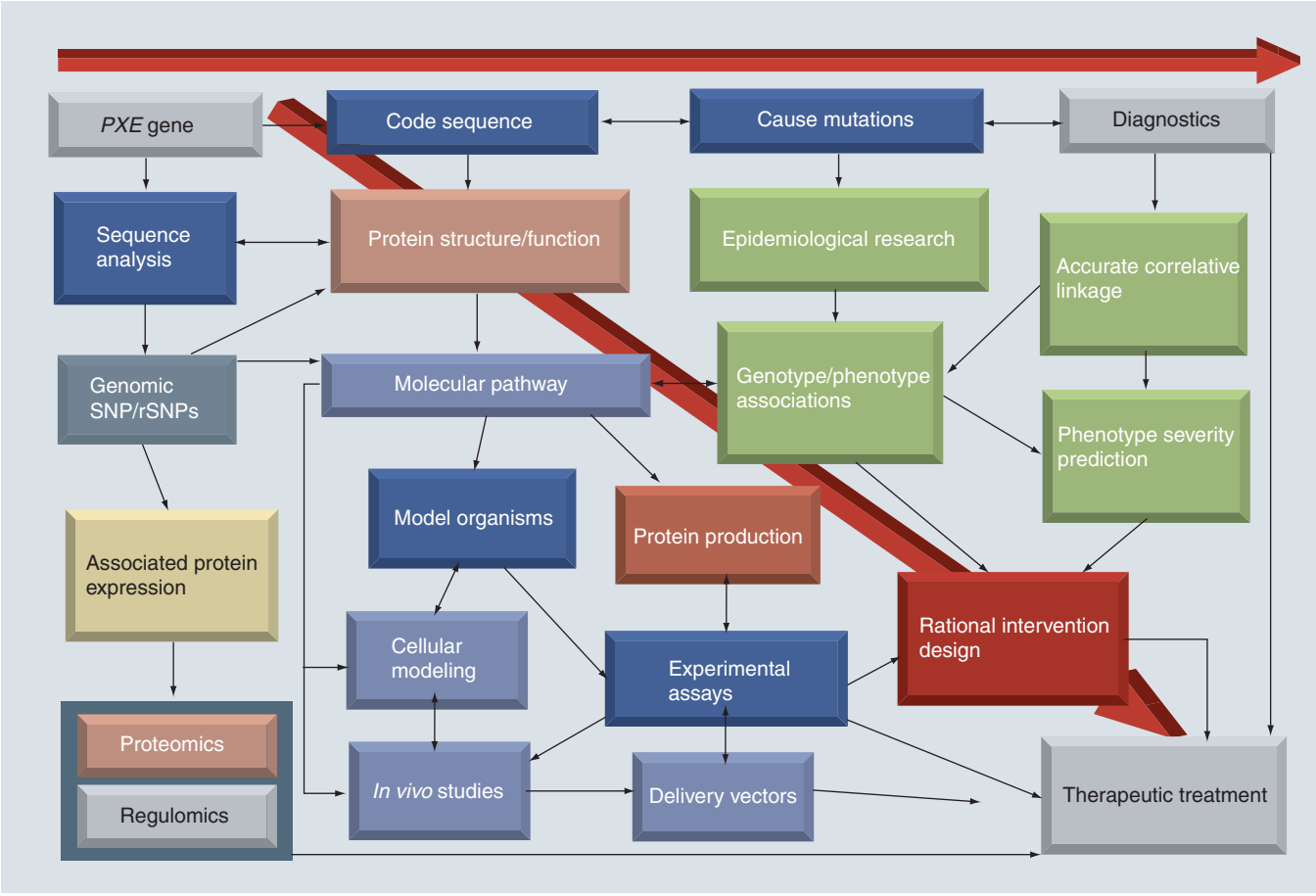

Figure 2. Solutions: data collection plus data integration plus time plus serendipity plus knowledge.

information. At the same time, depositing all the information emerging from the mapping of the human genome into the 'commons' – the National Human Genome Research Institute ([NHGRI] MD, USA) allowed open access to this resource – created a landmark shift in biomedical research; it is one that has not finished rippling throughout the biomedical field. Novel ways to openly access information in the age of information abundance will be a major transformative tool in the quest to leverage genetic information for better human health.

At Genetic Alliance, we build systems that enable individuals, communities and organizations to create new solutions that share infrastructure and resources. The Genetic Alliance BioBank [107] is one example, allowing DAOs to bank biological samples and clinical data in a networked repository, providing all of the documentation, training, freezers, templates and software necessary for a state-of-the-art resource. In another example, working with communities to build an online customizable guide to collect family health history has led to the development of systems that enable families and communities to manage their health in significant ways. As yet another example, Genetic Alliance is conducting surveys and focus groups to understand the impact of the information learned in the USA newborn screening (NBS) program as a tangible experience of engaging in genetic testing on a population basis. If analytic validity for screening can be increased, thereby minimizing false-positives and -negatives, it could provide a basis for population-based registries and longitudinal follow-up, as is being tested in some states, such as Michigan, USA [108]. We are very interested in continuing to develop a systemic approach to therapeutic development, but see the same major impediments that other stakeholders have examined: the 'valley of death' – the gap between the traditional finishing point of grant-supported academic research, and compounds ready for industry to license or venture capitalists to back [21]. This includes difficulty in creating assays that allow high throughput screening, the high risk of failure in lead development and combinatorial chemistry described above, and a general lack of cohort readiness to validate clinical end points and test drug efficacy.

The greatest impact on the complexities of drug development that the DAO community can make is in building cohorts. These should be well-characterized populations, even small ones for rarer conditions, that provide samples, clinical information and medical records. This would greatly aid the development of clinical end points and intermediate biomarkers. We work with the various DAOs to create systems for cohort development, natural history studies, and ultimately clinical end point and biomarker development. It is also critical that new information technologies are employed to allow individuals to consent, reconsent and control their privacy preferences.

Age of unprecedented information abundance & availability

In the current information age, systems throughout society no longer depend on material goods to engage in transactions. There is an abundance of easily accessible information that is increasingly available online. Theories such as the Long Tail (Figure 3) tell us that when there are many choices with low distribution costs, 'customer' transactions result in a power law distribution curve [22]. In 'long-tailed' distributions, a high-frequency or high-amplitude population is followed by a low-frequency or low-amplitude population that gradually 'tails off' asymptotically. The events at the far end of the tail have a very low probability of occurrence. While much attention has been paid to the 20% 'head' of the curve, the 80% 'tail' distribution is actually most interesting in any economy with decreasing costs for information management. Good examples of the head of the curve are big box stores, stocking items that satisfy 20% of the customers, since they represent the most 'common' customers. However, iTunes [109] and Amazon [110] meet the needs of millions of customers with uncommon or rare interests, and do a larger aggregate business for less cost. This is applicable to both rare conditions and common conditions stratified by genetics and genomics. This trend, coupled with Moore's Law (the number of transistors that can be placed inexpensively on an integrated circuit doubles approximately every 2 years [23]) and Metcalf's Law (the value of a telecommunications network is proportional to the square of the number of users of the system [24]), affords us a vision of a future where it is possible to collect and manage hundreds of thousands of variables from billions of people. Could it be that we are on the brink of being able to manage biomedical information in such a way that the cottage-industry structure (fewer than 25% of US office-based physicians use partial electronic medical records [111]), with its archaic regulatory systems and lack of adequate reimbursement, will no longer be state-of-the-art?

Parts of biomedical research and healthcare will be transformed by societal trends like those detailed above. As barriers to participation are lowered, new paradigms will be born. DAOs have longed for this new age. However, this will be a watershed moment. Some DAOs have been short-sighted about changing their business models and may soon see the same effect as other industries, such as publishing and music, which have been faced with the advent of online commerce. Siloed, single disease efforts without extensive Web 2.0 solutions will languish in the new era.

Law of finite biology

Randy Scott, PhD (Genomic Health, CA, USA), added his own law to Moore's and Metcalfe's: the Law of Finite Biology. A finite number of genes make up all organisms, and like a puzzle, deciphering them will become easier with increased knowledge [25]. Complexity will collapse at an accelerating pace, and biology is ultimately more measurable. Therefore, it is not surprising that the metrics by which to measure change are sought in the management of health and disease information. The most sought after metric for DAOs is disease-free survival with a high quality of life. This is the ultimate clinical end point, and DAOs strive to find a biomarker that lives up

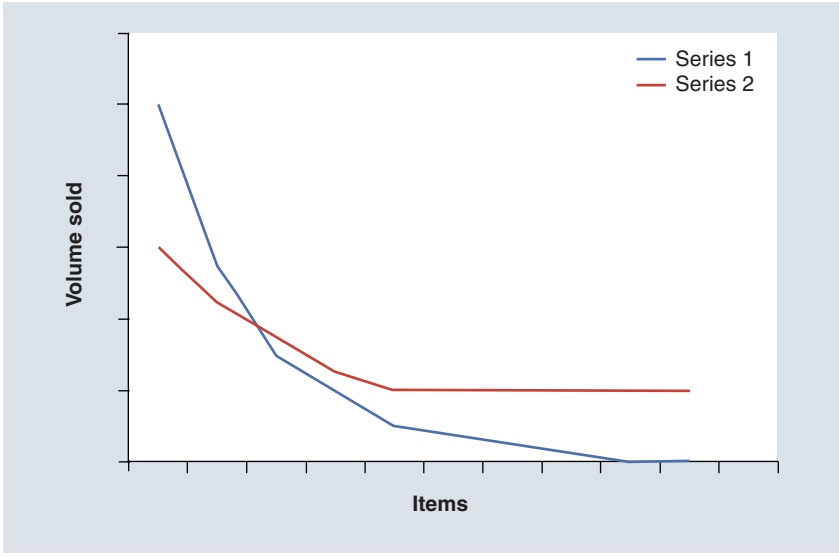

Figure 3. An example of a power law graph. To the left are the few products that dominate a market (also known as the 80–20 rule). The tail becomes bigger and longer in new markets (such as online bookstores and music stores).

to this standard [26]. However, this 'Holy Grail' may be unattainable, since genes are not destiny and environmental influences are not finite. Still, it is critical that numerous appropriate surrogate biomarkers are available to assess clinical validity and utility for tests and treatments. Perhaps, given the finite nature of biology, analytic validity is the easiest attribute of biomarker development to attain. The movement into the clinical realm, the grey area between biomarkers and end points, deserves attention. Choosing correct clinical end points and translating them back to primary and secondary biomarkers or surrogates is an endeavor that is perceived differently from the point of view of the consumer versus the researcher.

Several continuums that are usually perceived as dichotomous

Disease Advocacy Organizations, in their single-minded desire to do well for their members – those affected with a specific condition – often seek extremes: a cure, direct evidence that something is effective and/or zero treatment toxicity. They often have a strong need for systems to be binary – go/no go. This is often not possible within the complexity of these systems. These are robust extremes of continuums that need to be viewed with tempered urgency, mindful of the iterative nature of biomarker development.

Those who live with disease desire retention or restoration of a high quality of life, even with, and because of, increased survival. While this is not at all unreasonable, and in fact should be the major focus of all biomedical research, this does not always provide an immediately useful biomarker. On the other hand, intermediate biomarkers that are not truly indicative of health benefit are difficult for patients to understand. These two perspectives are not ubiquitous, but the tension between them reveals a critical point. Understanding this juncture would help to focus on relevant secondary biomarkers to either accumulate enough of them so as to determine efficacy and utility of a drug, or to bring a drug to the point where a primary biomarker could be used.

Direct evidence, created through the highest standards of the Agency for Healthcare Research and Quality's Scoring System for Evidence-Based Medicine, including double-blind, randomized, control trials, is certainly most ideal strictly from the point of view of the science. However, as we look to accelerate the discovery of effective treatments, this level of evidence is often not available, or is simply too costly or too difficult to achieve. This is particularly true in both rare diseases and in the more stratified population segments who may respond to a particular drug, even in a common disease cohort. Thus, there is a need for many levels of evidence. Decisions regarding appropriate levels of evidence should be titrated against the various attributes of the condition, the cohorts available, quality of life issues for those affected by the disease and the morbidity and mortality of the disease.

Another seeming dichotomy that must be addressed is the apparent conflict between designing individualized medicine and prescribing it on a population basis. Accuracy increases as cohorts are recruited in greater numbers and are more carefully characterized. There is a great need for a very large cohort study in the USA, similar, but probably greater in number than those recruited by other national biobanks, simply because the USA has a larger and more diverse population. Systems of self-management such as those used on Facebook [112] and Match.com [113] will be useful in this regard. It will also help if these systems allow individuals to decide how much of their information will be available, how much will be withheld and in which projects they wish to participate. The issues surrounding dynamic reconsenting and Phase IV surveillance should be more readily solved through systems using social networking, like those in widespread use for commerce, causes and social interaction. It is possible that these national systems could be linked together to create an international cohort. It will be critical that all information provided by individuals and their healthcare providers is subjected to verification. The burden of verification should increase as information is used more and more to stratify cohorts for discovery around treatment decisions.

Risk-averse nature of society places a greater burden on regulatory systems & reduces the possibility for success

As was described almost 30 years ago, 'American society is risk averse because it is a litigious society' [27]. The increasing trend of risk aversion in the culture has created regulatory systems that are not athletically flexible for risk management. In other words, there should be mechanisms, particularly in diseases of high morbidity and mortality, for biomarker developers to create biomarkers with more inherent risks. Of course, these risks need to be mitigated as much as possible, but in certain instances, the risk associated with certain death from a disease

exceeds the risk of treatments, even unproven, fairly lethal ones. By association, the biomarkers for diseases with high mortality need not be held to the same standards as those associated with conditions that have low morbidity and are common. Companies, universities, investors and their institutional review boards have a difficult time assuming risk – whether financial or medical – because the rest of the system shirks responsibility for risk, and it is not balanced across all entities. Thus, these organizations seek ways to reduce risk, but are not able to mine the dynamic tension that new social systems allow. In other words, these new systems will provide access to more people, allowing faster cohorts to be built than ever before. However, if industry, universities and investors are not able to share risk – for example, in flexible, regulatory schema, or in allowing individuals to decide when and how they want to be involved in trials – then they cannot innovate at the rate the disease community desires. In the new order, the sum does not have to be zero; there is room for win–win scenarios in systems that do not rely on materials and scarcity.

Need for new methodological approaches

All of this indicates a need for a new paradigm that incorporates new technologies, develops and aggregates evidence in an incremental way, and also considers the ultimate end goals of health outcomes. The sense of urgency embodied in many DAOs, coupled with the information technology culture, will necessarily open digitized systems in a disruptive way. New value propositions will be created and additional solutions born from next-generation information management tools. This diverse and networked consumer community will make use of digital technologies and surpass its current leaders. A Long Tail system does not need 'hero' leaders any more than the person selling his/her used books on Amazon needs to know Jeff Bezos, Amazon's founder. These information support systems will assault the conservative and insular systems of a paper-based environment of medicine and clinical practice. They will deliver tools for nonexpert users to derive the maximum value (with a user defined 'value') from virtual resources and bioinformatics to answer and/or solve medical questions, without a traditional medical intermediary filtering personal health information. To some, this sounds like a prescription for chaos that corrupts medicine as it should be; for others, this system can build biomarkers that will be useful and adaptive.

These expanding networks will create new lexicons that will be brought to bear and to capture, and take full advantage of Scott's Law. They will map the new options, alternative avenues and informed choices. These will be powered through automated, analytical and intelligent machine software creating a sophisticated convergent delivery of specialized information. This will include medical literature retrieval and improved search results – optimized on controlled vocabularies derived within very narrow and highly technical fields of genomic science, medicine, therapeutic options and clinical trials as well as the arcane structures of US healthcare delivery – to inform consumer-centered medical information. Ultimately, these will produce radical changes in the management of biomedical information and informed decision-making on the part of all stakeholders from patients to healthcare providers, payers and researchers.

A reorientation to an individualized approach to disease characterization and patient management provides a clear avenue for real-time directive intelligence, evidence-based approaches and clinical management alternatives that can incorporate cost–effectiveness trade-offs and risk:benefit calculations that are truly personalized. This new orientation of informatics platforms and clinical decision support tools could usher in a new era of relevant biomarkers that will allow mass-customization of effective systems that can prioritize system level efficiencies. This may happen first in disease management, then in wellness, and lastly in disease prevention approaches.

These highly iterative, self-learning, adaptive systems will accelerate what could be considered, and perhaps what the public will come to demand and expect from a modern digitized healthcare delivery approach, 'current best practices'. These tools will emerge organically at first as freeware, widgets and communal resources, created by small communities of experts, even beyond what the leaders themselves envision. Some of these already exist in online solutions such as Google Health [28], PatientsLikeMe [29,114], Duchenne Connect [115] and Private Access [116]. These tools and emergent informatics platforms will coalesce with internet-based utilities and centralized intelligent algorithm servers. This will enable the necessary aggregation, and it will reorganize information, users and self-identified patients, to develop iterative biomarkers. This emerging consumerism in health and medicine could be the most critical disruption to the entrenched and highly bureaucratic legacy systems that characterize the healthcare delivery system today.

This revolution will permit a national surveillance system for pre- and post-treatment analysis, similar to what is done for infectious disease, but surpassing it. In a society that is able to tie buying patterns derived at the point of purchase with targeted advertising, and as a result, attempt modification of buying behavior, we should be able to correlate biomarkers with treatments. Claims data can easily be linked to prescriptions and, just as individuals report their software errors automatically online to Microsoft (WA, USA), they can report their reactions, biometrics and even environmental data.

As personalized medicine and pharmacogenomics disrupt the usual process for drug development, the precompetitive part of the pipeline will increase, as we saw it increase during the sequencing of the human genome. Information about failures in the pipeline, and even analysis of successes, must be more frequently shared. In addition, it is possible that innovation, discovery and even profits will increase with a larger precompetitive 'commons'. FIGURE 4 shows a potential new line for the precompetitive section of the pipeline.

Federal agency activities should be coordinated. The National Institute of Standards and Technology ([NIST] MD, USA) should be involved in creating guidances for standards for analytic validity, thereby building the foundation for solid science that can be compared and replicated across laboratories. The National Institutes of Health (MD, USA) could require that researchers receiving grants build into their projects regulatory sufficiency, such as using NIST guidances and FDA-approved products and processes in their experiments, so that the right rigor is in place for regulatory approval at the end stage. Federal agencies also have information that could be coordinated and mined for value. For instance, over the past 25 years, the FDA Office of Orphan Products Development received 2622 requests for orphan drug designations, and awarded that status to 1850 products. It would be very interesting to examine the 772 products that did not receive designation. Certainly, there will be some scientifically untenable applications, but there may also be products that are now promising and can be repurposed to a stratified population, or products that simply did not have follow-through because of other, nonscientific issues.

All of these methods can create a stronger and more scientific basis on which to build quality control and assurance of biomarker determination. Providing quality information to laboratories creating assays will lead to more precise biomarkers, which in turn lead to more refined drug development with regulatory clarity. Biomarker validation, whether cellular or clinical, will be greatly aided by well-characterized cohorts and their biological samples. The patient's sensibility of appropriate clinical end points is not the same as that of the test or drug developer or the regulatory agencies. In its extreme, the patient wants a restoration of health, with no traces of disease. The drug

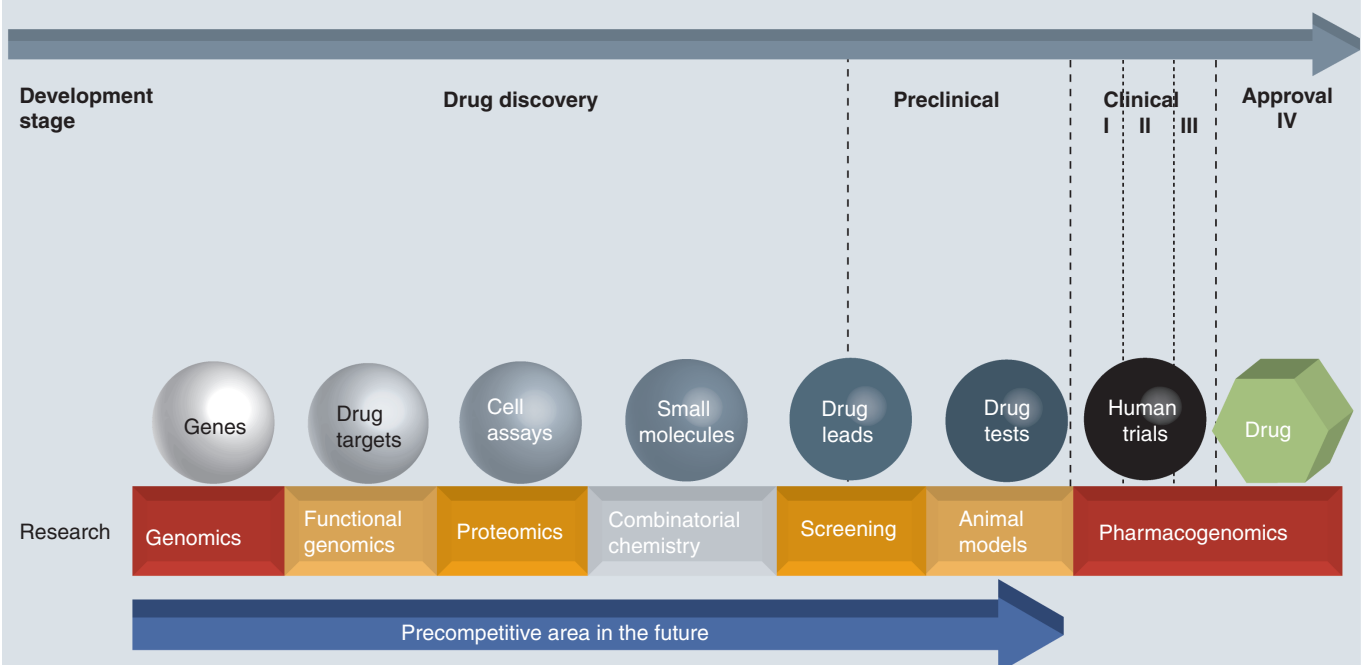

Figure 4. Drug discovery and development – expanded precompetitive area in the future.

developer wants indication of meaningful biological activity that mitigates some manifestations of the disease, such that the payers will reimburse for the drug. The regulatory bodies want safe and effective treatments, but at this time have no clear definitions of clinical validity. The drug development system today has no mechanisms for validating biomarkers and clinical end points that meet the needs of all of these entities.

Novel methods, such as aid to pharmaceutical companies to mitigate some of their risk as they consider stratifying cohorts, should be considered. This could come in the form of incentives to increase the submission and use of pharmacogenomic data. The current voluntary submission system for the FDA is a start [30], but perhaps this information, 'deidentified' and then made publicly available, would eventually be more useful overall.

Finally, while basic discovery research is well supported by major funding agencies throughout the world, there is little support for validation, in either common or rare conditions. For common conditions, validation would have support if it were well integrated into the pipeline. For rare conditions, governmental and philanthropic support is critical. The NIH have made a good start with programs such as the Rapid Access to Interventional Development (RAID) and the molecular libraries program, with the National Chemical Genomics Center (MD, USA) as the flagship for chemical probe development. In the UK, the Seeding Drug Discovery [21] program takes a giant step. But a comprehensive, global

Executive summary

- In the future, we will know what causes disease and be able to treat it.
- The translation of genetic information requires that therapies be measured against appropriate clinical end points.
- The process of developing these end points and testing them is fraught with a high failure rate and enormous expense.
- Disease Advocacy Organizations (DAOs) make meaningful contributions in the development of therapeutics from cohort development to actual drug discovery.

Firsthand experience of DAOs' efforts

- The DAO for pseudoxanthoma elasticum discovered and patented the gene, established a biobank and registry, and is working towards a therapeutic.
- Many DAOs work together to accelerate therapeutic discovery.
- Genetic Alliance, a network for these organizations, builds tools for them and transforms health through genetics.
- DAOs need to harness new information technologies to increase effectiveness, including systems to dynamically consent individuals to participate in registries and trials.

Age of unprecedented information abundance & availability

- The Long Tail theory describes a power law distribution curve that describes rare diseases and rare variants in common diseases.
- Moore's Law and Metcalf's Law contribute to the ability to manage large amounts of complex information including biomedical information.
- DAOs must adopt new systems for managing information electronically.

Law of finite biology

- A finite number of genes make up all organisms.
- It is therefore possible to measure genes and their effects, but environmental effects are not finite and make identifying biomarkers difficult.
- Defining useful clinical end points is essential in drug development.

Several continuums that are usually perceived as dichotomous

- DAOs often seek extremes: cures and zero toxicity from treatments.
- Understanding the tension between these two extremes could reveal good secondary biomarkers.
- There is a need for a large cohort study in the USA and other nations, and by using social networking tools, international cohorts could be built in which the participants control access to their information.

Risk-averse nature of society places a greater burden on regulatory systems & reduces possibility for success

- American society is risk averse.
- There should be a flexible regulatory paradigm to allow for taking risks on diseases with higher morbidity and mortality.

Need for new methodological approaches

- New information technologies will allow consumers to derive their own value from biomedical information.
- Highly iterative, self-learning, adaptive systems will accelerate derivation of best practices.
- Information aggregation with consumer control of information at its core will eventually permit a national surveillance system for pre- and post-treatment analysis.
- The precompetitive section of the drug development pipeline will increase, creating a larger 'commons'.
- Federal agencies' activities should be coordinated.
- A stronger and more scientific basis on which to build quality control and assurance of biomarker determination is needed.
- Validation must be supported in the future in the same manner that discovery was in the past.

approach is needed, with a scientifically driven coordinated program combining the expertise and resources of government, industry, regulators, payers and DAOs.

Conclusion

Biomarkers are a complex network of redundant and interactive pathways. In the context of environment, these finite, but very complex systems, will be difficult to quantify, making it difficult to then create metrics that are meaningful. Through the use of new information technologies, shared resources – including negative information – and increased participation of leaders of disease-specific advocacy organizations, substantial headway should be possible. Biomarkers might be the simplest pathway to disrupt medicine to the point of accelerating its realignment with a progressive society.

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