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Renal Pre-Competitive Consortium (RPC^2): discovering therapeutic targets together

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Despite significant effort, patients with kidney disease have not seen their outcomes improved significantly over the past two decades. This has motivated clinicians and researchers to consider alternative methods to identifying risk factors, disease progression markers, and effective therapies. Genome-scale data sets from patients with renal disease can be used to establish a platform to improve understanding of the molecular basis of disease; however, such studies require expertise and resources. To overcome these challenges, we formed an academic–industry consortium to share molecular target identification efforts and expertise across academia and the pharmaceutical industry. The Renal Pre-Competitive Consortium (RPC^2) aims to accelerate novel drug development for kidney diseases through a systems biology approach. Here, we describe the rationale, philosophy, establishment, and initial results of this strategy.

Introduction

Deaths from chronic kidney disease (CKD), unlike most noncommunicable diseases, increased by nearly 20% over the past 20 years [1]. This represents one of the most concerning, global, public health challenges of our day. In addition to affecting between 8% and 16% of the worldwide population, CKD [2–4] increases risk for end-stage kidney disease (ESKD), cardiovascular disease (CVD), and death [5]. The 2017 annual report of the United States Renal Data System lists the total Medicare spending on both CKD and ESRD at more than US$98 billion [6]. Beyond the high financial costs, patients endure poor quality of life and premature death.

Therapeutic interventions have been shown to slow the progression of CKD and reduce its associated CVD risk in some patients [2]. Unfortunately, advances in outcomes have not occurred because of limited therapeutic options, and no new therapeutic principles have been introduced over the past two decades. Early stages of drug discovery are historically underfunded in the industry because of the increased costs of later-stage development and clinical trials. Additionally, there is a limited ability to identify patients at high risk of losing renal function in early CKD and to provide them with safe and effective treatments tailored to their individual disease. Convergence of these issues led to a shifting paradigm in drug development and the formation of academic and industry partnerships in kidney disease in Europe and North America. Here, we report on our experience with RPC^2. This public–private partnership for precompetitive drug discovery is a collaborative, shared resource initiative that aims to accelerate the discovery and development of novel therapies for renal diseases by combining insights from academia and industry, using an integrative systems biology approach to identify key pathways for therapeutic attack (ASN INFO20, 2016; www.asn-online.org/education/kidneyweek/2016/KW16_Onsite_Program.pdf; ASN INFO15, 2017; www.uofmhealth.org/news/archive/201602/u-m-announces-chronic-kidney-disease-consortium-leading).

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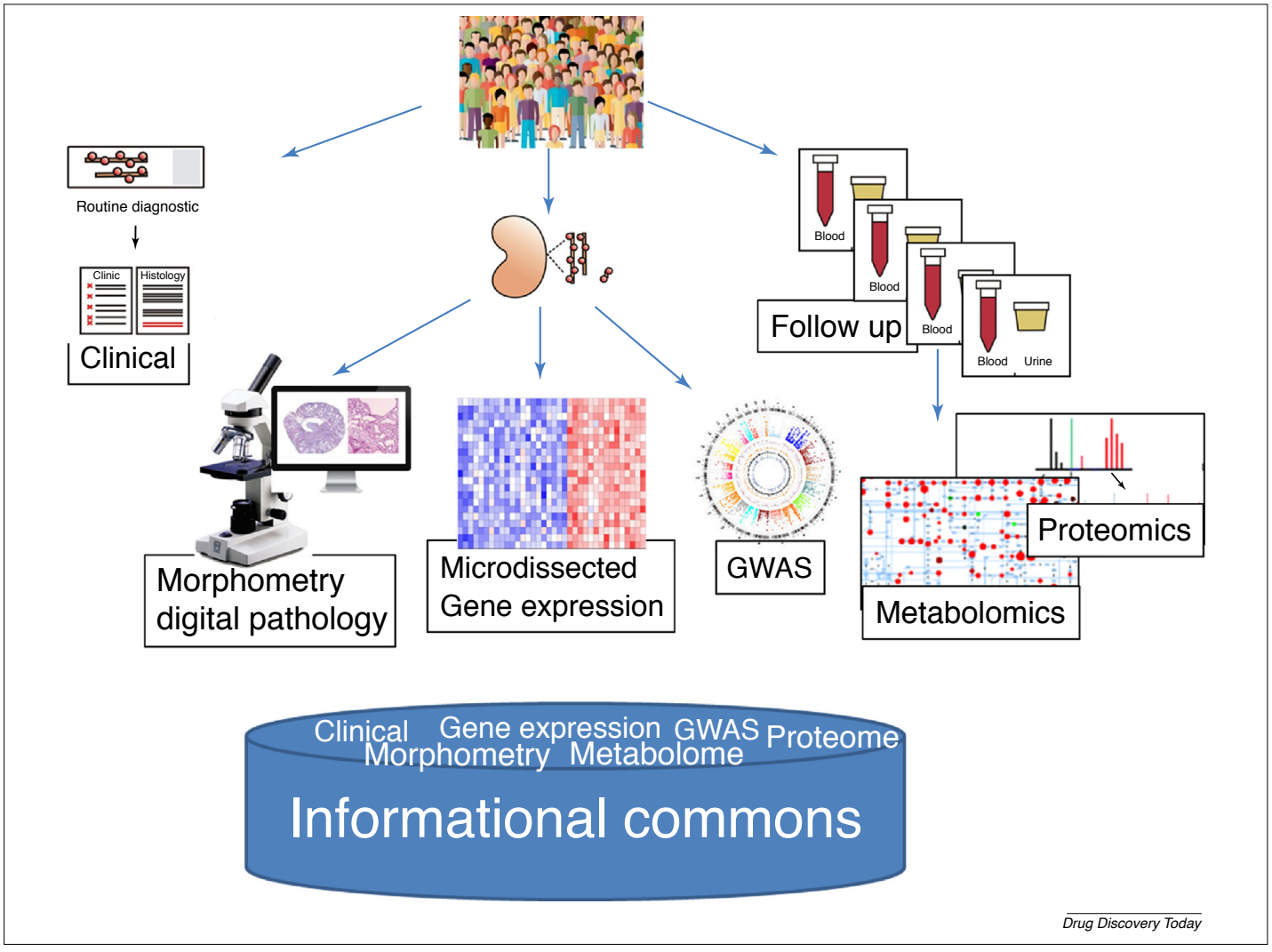

FIGURE 1

Systems biology approach: depiction of the integration of a variety of data types into an informational commons for interrogating data in a systematic approach. The different data types, along with clinical features, allow researchers to understand the molecular systems at play in diseased patient samples.

Our collaborations with pharmaceutical partners AstraZeneca, Eli Lilly and Co., Gilead Sciences, MedImmune, and Novo Nordisk, as well as academic experts within the University of Michigan, allow all parties to benefit from the mutually complementary strengths (Fig. 1), while diversifying cost and risk. Early discoveries and large-scale efforts by academia are not left on the shelf, but rather leveraged by active programs within pharma to help to prioritize novel compound–target pairs for development. Furthermore, modeling renal disease along the full spectrum of the genotype–phenotype continuum sets the stage to define predictive biomarkers and validated disease models. This establishes the foundation for pharma partners to advance compounds through discovery to clinical trials and, ultimately, to patients. Finally, the discovery and validation of predictive biomarkers helps to identify the appropriate patients to treat, with a specific agent at the appropriate time during disease progression to elicit the optimal target response.

Systems approach to renal disease

Until recently, drug development had used an expensive trial-and-error, target-centric approach to identifying therapeutics and tested compounds passing preclinical evaluation in large populations of patients believed to have a homogeneous disease defined by histopathological classification systems. Given the underlying mechanistic heterogeneity of the renal diseases, this approach often failed. Drugs implemented might have targeted a pathogenic mechanism, but if this pathway is only active in a small section of the trial population, the study will inevitably fail. Furthermore, the methods used to detect individuals with disease and progression rely on estimated glomerular filtration rate (eGFR) and urinary microalbumin excretion (albumin:creatinine ratio; ACR). Unfortunately, by the time these biomarkers are detected as abnormal, significant structural damage has already occurred and it is unknown whether responses would be similar or whether damage is reversible through therapeutic intervention [7,8]. Without clearer understanding of the molecular pathogenesis of the disease and risk factors for progression, the odds of discovering effective therapeutic options are rigged against both scientists and patients.

As limitations of current therapeutic options and classical drug discovery approaches were recognized, strategies to define human renal disease in molecular terms emerged. The vision to understand and dissect the molecular basis of CKD began more than 20 years ago, with standards developed for renal biopsy sample curation, profiling, and data sharing [9,10]. Many of

these efforts and associated data have matured to the point that the discovery of active pathways, new therapeutic targets, predictive biomarkers, and molecular disease classification have become a reality for CKD [11].

Nephrologists have an advantage in the practice of medicine because they often take multiple and varied samples, including diseased tissue samples, urine, and blood (Fig. 1). Each sample can be analyzed using a variety of molecular profiling techniques, including next-generation sequencing for RNA species, targeted and untargeted proteomics and metabolomics, to name the most prominent approaches. Each patient also has a variety of clinical parameters collected or calculated from tests conducted on these samples, including glomerular filtration rate, proteinuria, and histological features captured using digital pathology. Furthermore, laboratory model systems are being carefully mapped using genome-scale profiling of the molecular pathways regulated in diseased renal tissue and can then be deployed selectively to test the pathways they share with the human disease states. All of these advances provide the key components of implementing a targeted therapeutic approach to support the main goals of the consortium.

In one example of a systems approach using integrated data, Ju *et al*. clearly demonstrated the role of urinary epidermal growth factor (uEGF) in predicting the progression of kidney disease [12]. Although still unclear, the impact on patient outcomes from using uEGF is predicted to be significant and studies are underway to determine it.

Another example of using an integrated systems biology approach to advance a compound into clinical trials for kidney disease is a JAK/STAT pathway inhibitor [13]. This compound was successfully approved in many countries for the treatment of rheumatoid arthritis. After discovery of the active JAK/STAT pathway in genomic data of samples from patients with diabetic nephropathy, the JAK/STAT pathway inhibitor was repurposed and Phase II clinical trials were initiated for diabetic nephropathy. Not only is this the first example of precision medicine targeting patients with diabetic nephropathy, but it is potentially also the first new chemical entity for kidney disease in 20 years. Although there is still much work to be done, initial Phase II results were positive in a dose-dependent manner for key indicators of diabetic kidney disease [14]. The translation of a discovery using large cohorts of patient samples through laboratory and animal testing to clinical trials set in place the foundation for the formation of RPC^2, with the ultimate goal of accelerating the development of novel renal disease therapies through active collaboration between academia and industry, in a manner similar to the JAK/STAT pathway inhibitor story.

Processes of establishing RPC^2

The JAK/STAT success story was the main driver behind the pitch for establishment of the consortium. In addition, previous collaborations with the pharma industry revealed similar questions across the industry best answered in a precompetitive space: What is the spectrum of therapeutic targets in CKD? How do we recognize a biomarker of progression? How can we best repurpose in house compounds for development in the right type of kidney disease? And so on.

Once there was initial interest from three partners in a precompetitive consortium, the arduous task of designing the framework and the legal language of the agreement began. The structure (described below) and resources were aligned relatively easily, whereas the contractual framework took substantial effort to align three pharma partners and the university.

Key establishment parameters included legal documentation to which the partners unanimously agreed. This was a significant hurdle during initial negotiations. However, once established, the common language has been easily extended or amended on a yearly basis. Having had the rigor of three pharmaceutical partners agree on language has set the baseline for new partners. Indeed, the consortium has grown from four to five partners without changing the contract language. Additionally, the plan is for slow, measured growth, adding partners while maintaining the desire to be a nimble decision-making group. Members are added following close scrutiny by the scientific director and business director with regard to perceived fit with the existing partners and willingness to contribute to the consortium. In this way, the RPC^2 might experience a flux of partners because individual partner companies might change their own direction and decide to exit the group.

Another foundational piece of the contract language included the absence of individual intellectual property (IP) rights for discoveries within the consortium, which is key for any precompetitive operational model. Any targets or pathways with potential for IP will need to be fully characterized, validated, and developed in a competitive space outside of the consortium.

An important piece of the network concerns sharing the resource burden equally among partners. Resource contributions from the private partners support the scientific expertise deployed towards the common aims of the consortium.

A systems-biology approach has many potential advantages to finding new therapies, but requires extensive expertise in a variety of diseases and technological areas. The partners in the RPC^2 share the vision, resources, and expertise, and also contribute to the common goals of the consortium, thus leading to successful, precompetitive activities and understanding basic molecular characteristics of disease and progression. All partners share in determining the focus of the research of the consortium through a joint steering committee with equal representation of all partners to ensure that each one's interests are addressed. At any point, the joint steering committee can convene to discuss a change in the scientific direction of the consortium with voting by each partner. This was purposely designed into the establishment of the group to meet the changing needs of the pharmaceutical industry. To date, the consortium has enjoyed unanimous alignment on the direction of the research efforts. Finally, each partner has dedicated staff to the consortia to establish trust and beneficial relationships. Establishing the consortium in this way has led to contagious data and expertise contributions from all partners.

Project proposals were generated by scientists, then reviewed and prioritized by the steering committee. Following the acceptance of the initial ten projects, scientists volunteered to colead the various project teams. Leadership and team membership were determined by interest and expertise. With shared expertise and interaction across a normally competitive space, the consortium has observed the many ways in which the larger research community can be strengthened and how this effort can lead to accelerated advancements (Fig. 1).

The current direction of the consortium is to utilize a genome-wide analysis approach to discover potential targets for therapeutic intervention and to investigate biomarkers to understand the molecular classification, stage, and progression of kidney disease. This approach allows industry to work freely together in a precompetitive manner where individual target and drug pairs have yet to be defined. Using the genome-scale approach and specific contractual wording removes IP concerns that would restrict activity among industry collaborations. Indeed, the consortium has already experienced accessible data sharing between all RPC^2 members and active team collaboration to advance the

objectives of the consortium, accelerating the discovery and development of new therapeutics for kidney diseases.

Structure

Governance is effected through a joint steering committee comprising one voting member from AstraZeneca, Eli Lilly and Co., Gilead Sciences, and Novo Nordisk, and the scientific director from the University of Michigan. This committee serves to align the consortium on the direction of scientific pursuits, to approve and prioritize projects, as well as to approve budgets. Working groups were established early during the establishment of consortium as entities contributing to the knowledge and core data generation. Several of the teams have overlapping individual membership, which enables easy crosspollination of projects, whereby each project then enhances others. Working group membership and leadership might change over time as projects mature or take on new directions. The project working groups are led by senior advisors, from both the biology and bioinformatics fields and from both academia and pharma partners. They oversee, direct, and participate in the project work. These advisors bring new methods and ideas to working groups, ultimately improving processes and results. The specific roles of the partners in each working group are determined by their expertise and interest. The roles can span leadership, data contributor, analysis contributor, or observer, given their particular expertise brought to the project team (Fig. 2). In sum, the joint steering committee envisions applying an integrated approach to understanding the pathophysiology of CKD. The integrated approach is being implemented by the working groups. As mentioned above, the working groups are essential players in the RPC^2, driving projects forward by contributing ideas, methodology, and analyses.

Project working groups set up the framework for more seamless project management. Each working group essentially has a defined project managed by a project manager located at the University of Michigan. Weekly working group conference calls are held to assess project advancement and discuss next steps. This is done through commonly available teleconference communication software. Meeting notes are captured, actions identified, and all are shared across the project team members through a portal-based data-sharing tool. Communication was designed to be open and free flowing between all partners. Steering committee meetings are less frequent but held as needed via teleconference and face-to-face at least twice per year for frank discussions, data review, and future planning

Data sharing between all consortium members is a key component of the structure for RPC^2 and its industry–academia structure, existing in the precompetitive phase of target discovery (Fig. 2). An important aspect of an integrated approach in data sharing was the construction of an informational commons that enables the knowledge network approach (Fig. 1). This informational commons contains all of the data, including longitudinal data gathered across multiple patient visits. Important features of the informational commons include sound scientific curation, a standardized ontology, and easy access to the data for analysis. The consortium utilizes two software products that serve as informational commons and systems biology toolsets: Nephroseq^{TM} and tranSMART. Nephroseq is a web-based systems-biology toolset that houses mRNA expression data and the results of precomputed analyses on >1900

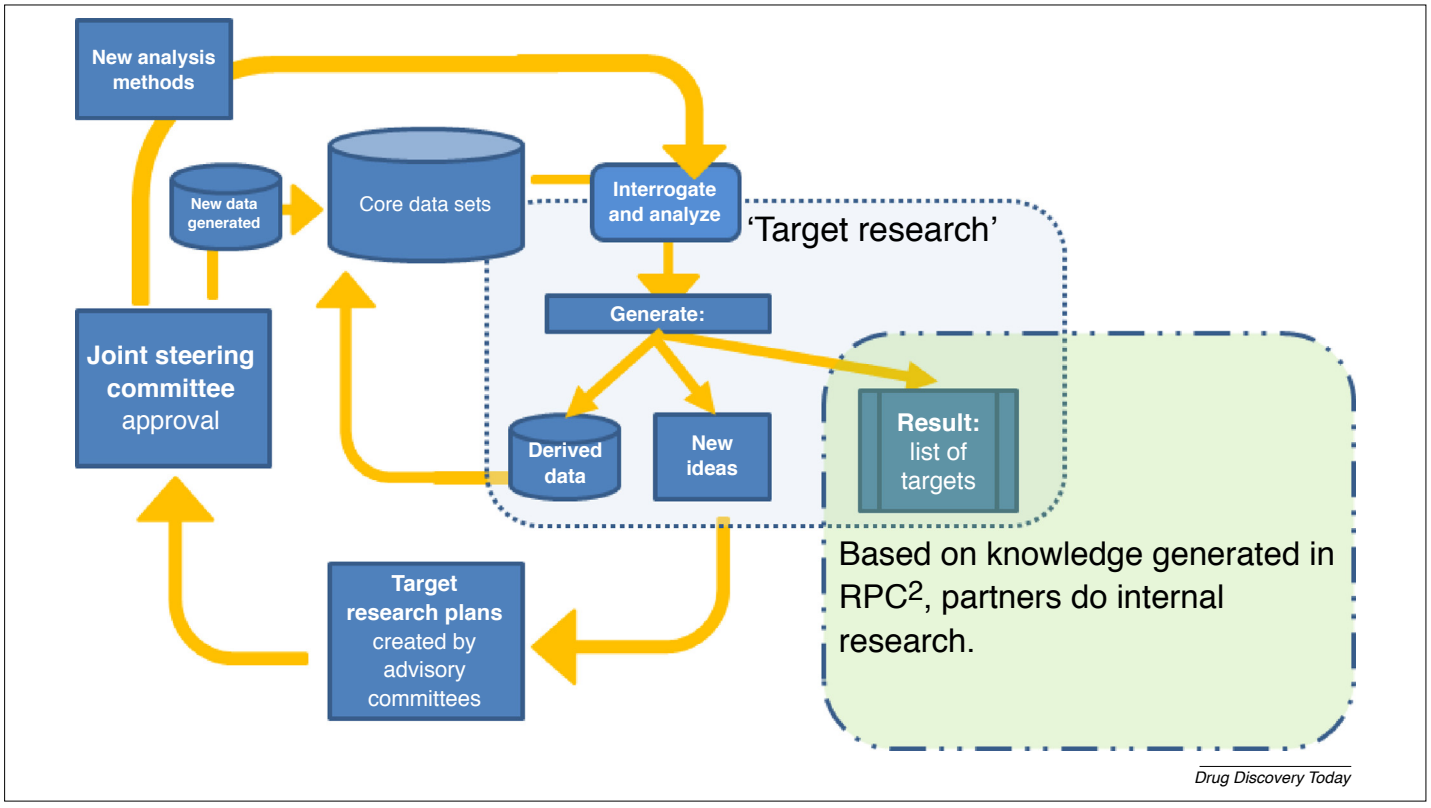

FIGURE 2

Renal Pre-Competitive Consortium (RPC^2) overview and governance structure: schematic describing the RPC^2 with core data sets as a central component for analyses by working groups and advisory committees. The analyses generate data, new ideas, and results. Data derived through interrogation of the core data sets can be added to the core. New ideas can be proposed to the joint steering committee for approval and prioritization. Lastly, all results are shared with all members of the consortium. These results can be used to generate new internal private projects behind each member's research walls (green-shaded area).

kidney samples across 25 kidney diseases. This tool is freely available to all academic labs and nonprofit organizations at Nephroseq.org. TranSMART (http://transmartfoundation.org/) is an open-source translational medicine platform that enables user-specified analyses across large kidney disease cohorts. These tools help to power an integrated approach that is critical to defining the varied diseases, in contrast to the simple application of histological features used in kidney disease medical practice today.

Initial results

Multidimensional disease definition is a critical first step in truly appreciating the breadth and depth of CKD. Furthermore, this definition dramatically impacts basic understanding of different diseases and the active pathways within each, enabling researchers to identify novel therapeutic targets and predictive biomarkers, as well as stratify patients for clinical trials. The RPC^2 is in its early stages and is investing in multiple project areas, including cell lineage-specific gene sequencing, in an effort to understand the various compartments and cell types contributing to disease. More specifically, the cell lineage working group defined mesangial, endothelial, and tubular-specific genes to extend the work of Ju *et al.* [15] who defined podocyte-specific genes through a predictive algorithm, followed by validation in the literature or laboratory studies. A common mechanism of diabetic nephropathy is mesangial expansion; the set of genes predicted to be of mesangial lineage were highly enriched in diabetic nephropathy glomerular samples that were subjected to microarray analysis. These data were confirmed in multiple independent data sets. The consortium is supporting research by pilot studies pursued by independent investigators to confirm results and generate a publication-worthy set of data. Once complete, the data will be published following the NIH data-sharing guidelines so that the larger renal community can further interrogate the data.

Morphometry and phenotypic characteristics of patient kidney biopsy samples can also be studied and related to gene expression data, thus enhancing the understanding mesangial gene expression in different kidney biopsies with particular morphometric measurements. The network analysis working group associated morphometric measurements with RPC^2-defined, activated, molecular pathways through a network analysis of CKD data sets. This analysis utilized both published and novel bioinformatics approaches to address the network of activated pathways. Using this method, the consortium identified disease-specific pathways, cross-disease networks, and kidney-specific tissue markers not necessarily associated with disease. Resulting pathways likely contain new targets for broad-spectrum kidney disease and disease-specific targets that might have application in patient stratification or diagnosis. The bioinformatics approaches can also be applied to data generated as part of the RPC^2 activities, such as a new, larger cohort of samples from patients with diabetic nephropathy profiled by RNA-seq. Results and methods are shared across all members of the consortium for each partner to competitively evaluate the data with respect to targets or biomarkers that may fit into their own portfolios.

RPC^2 working groups continue to generate data in a focused and measured manner, populating the informational commons to enable novel and robust analyses. A current effort within the consortium is to produce data from a variety of technologies, including gene expression, proteomics, and metabolomics, on biopsies and biological specimens for 100 samples that have longitudinal data. The goal of this effort is to generate a rich set of data to explore disease progression.

Concluding remarks

`It is our hope that work between various partners in both public and private sectors is so productive that this precompetitive framework is adopted not only elsewhere in nephrology, but also in other fields. The advantages of this effort and philosophy have both the potential to distribute and reduce the cost of effective and efficient research, and to decrease the time-to-identification of promising, therapeutic targets. With a richer pool of potential targets, pharmaceutical companies can focus resources not on discovery but on molecularly defined compound development for clinical trials in stratified patient subgroups, thus enhancing the speed to market. Although all these benefits are attractive for research entities, academic institutions, and public-sector investors and stakeholders, no-one stands to gain more from this personalized medicine approach than patients, who, in the end, will have the right medicine at the right time to treat their specific disease.

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