Mapping translational research in personalized therapeutics: from molecular markers to health policy

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Translational research is frequently used in the bioscience literature to refer to the translation of basic science into practical applications at the point of patient care. With the introduction of theragnostics, a new medical subspecialty that fuses therapeutics and diagnostic medicine with the goal of providing individualized pharmacotherapy, we suggest that the focus of translational research is shifting. We identify two bottlenecks or gaps in translational research for theragnostics: GAP1 translation from basic science to first-in-human proof-of-concept; and GAP2 translation from clinical proof-of-concept to development of evidence-based personalized treatment guidelines. GAP1 translational research in theragnostics is usually performed in traditional craft-based studies with small sample sizes and led by independent academic or industry researchers. In contrast, GAP2 translational investigations typically rely on large research consortiums and population-based biobanks that couple biomarker information with longitudinal 'real-life' observational data on a broad range of pharmacological phenotypes. Despite an abundance of research on the use of biobanks in disease gene discovery, there has been little conceptual work on whether and to what extent population biobanks can be utilized for translating genomics discoveries to practical treatment guidelines for theragnostic tests.

Keywords: biobanks, bioethics, biomarkers, General Clinical Research Center, theragnostics, personalized medicine, translational clinical research

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For biomedicine to improve human health, scientific discoveries must be 'translated' into applications at the point of patient care [101]. These applications can be information generating (e.g., genetic tests that aid in prediction of disease risk or the individualization of drug therapy) or therapeutic (e.g., new drug therapies and medical devices). Research that works between or at the interface of these two poles, that is molecular/preclinical investigations and practical applications in the clinic, is often referred to as 'translational research'.

As an applied science, translational research has a prominent focus on clinically-relevant product development. In the present age of knowledge-based economies and genomic technologies, translational research is increasingly visible and highly sought after by academics, research funding agencies and pharmaceutical or biotechnology industries [1–4]. However, despite its frequent use in the scientific literature there has been little conceptual work that maps out the process of translational research. For example, is such research a multistage process with several qualitatively different subcomponents? And what does translational research contribute in the context of recent trends towards developing personalized drug therapies? Furthermore, we suggest that translational research is currently being reshaped by the introduction of theragnostics, a term denoting the fusion of therapeutics and diagnostics [5,6].

Theragnostics indicates a fundamental transformation in pharmaceutical research and medical therapeutics, that is, a move towards codevelopment, and by extension, coprescription of diagnostic tests and drugs to individualize treatment regimens. Unlike routine clinical chemistry (e.g., plasma electrolyte measurements) or technology-driven biomarker approaches (e.g., genomics), theragnostics does not focus on a single technology platform or marker set, such as blood biochemistry or genetic polymorphisms. Instead, theragnostics relies on an integration of technologies for gathering information from different levels of the biological hierarchy. Thus, a theragnostic approach might include not only pharmacogenomic tests to identify the hereditary basis for individual or population variability in drug effects (whether based on genotype or gene expression) [7], but also include proteomic [8] and metabolomic [9] tests to discern the cellular proteins and metabolites, respectively, formed and degraded under genetic or (patho)physiological influences (**Figure 1**). For example, trastuzumab (Herceptin®) is a monoclonal antibody directed at the human epidermal growth factor receptor 2 (*HER2*) for use in patients with breast cancer

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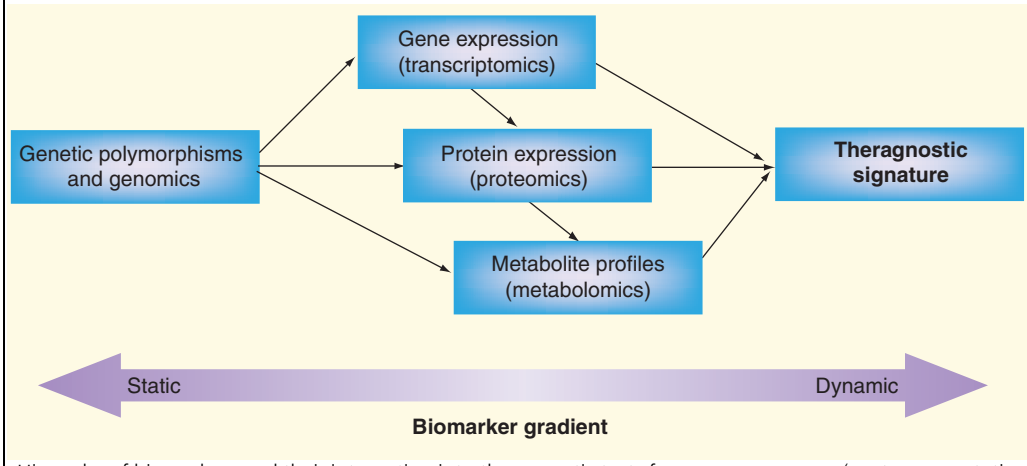
Figure 1. Hierarchy of biomarkers and their integration into theragnostic tests.



Hierarchy of biomarkers and their integration into theragnostic tests from gene sequence (upstream or static marker) to downstream (dynamic) markers on gene and protein expression or cellular metabolites.
A theragnostic profile is depicted as a synthesis of various biomarker tests that characterize an individual patient and their drug treatment outcome. The theragnostic profile may be heuristic in nature when only a singular biomarker is associated with treatment outcomes, while more mechanistic insights can be achieved when biomarkers from different levels of the biological hierarchy corroborate and complement each other (reproduced from authors' previous work [6]).

who are *HER2*-positive. Trastuzumab is widely claimed as one of the first generation of personalized medicines, because the drug is prescribed together with a theragnostic test to detect *HER2* overexpression; the test itself can use a variety of methods including gene (i.e., pharmacogenomic) and/or protein expression [10,11]. Theragnostics is thus a more holistic approach (and not a singular technology) to diagnosis and therapy selection than has traditionally been the case in biomarker research or medical practice.

This paper identifies and differentiates two bottlenecks or gaps (hereafter referred to as GAP1 and GAP2) in the conduct of translational research in the emerging field of theragnostics. There is a major gap, GAP1, in the translation of basic science discoveries to first-in-human (FIH) proof-of-concept [12]. A second serious gap, GAP2, occurs in the transition from clinical proof-of-concept to the development of appropriate treatment guidelines and science policy. We suggest that resolution of these bottlenecks or gaps requires distinct research aims, resources and study designs. For example, research directed at GAP1 may require focused small sample size academic or industry-sponsored studies [13–15]. In contrast, GAP2 translational research would require large-scale longitudinal population databases on observational 'real-life' treatment outcomes, an adequate understanding of professional responsibilities in disclosure of genetic test results, as well as core technical biomarker competency to explain variability in drug effects [16–19]. These gaps in translational research are collectively sufficiently important for the US FDA to have the view that, "the applied sciences needed for medical product development have not kept pace with the tremendous advances in the basic sciences. The new science is not being used to guide the technology development process in the same way that it is accelerating the technology discovery process" [12].

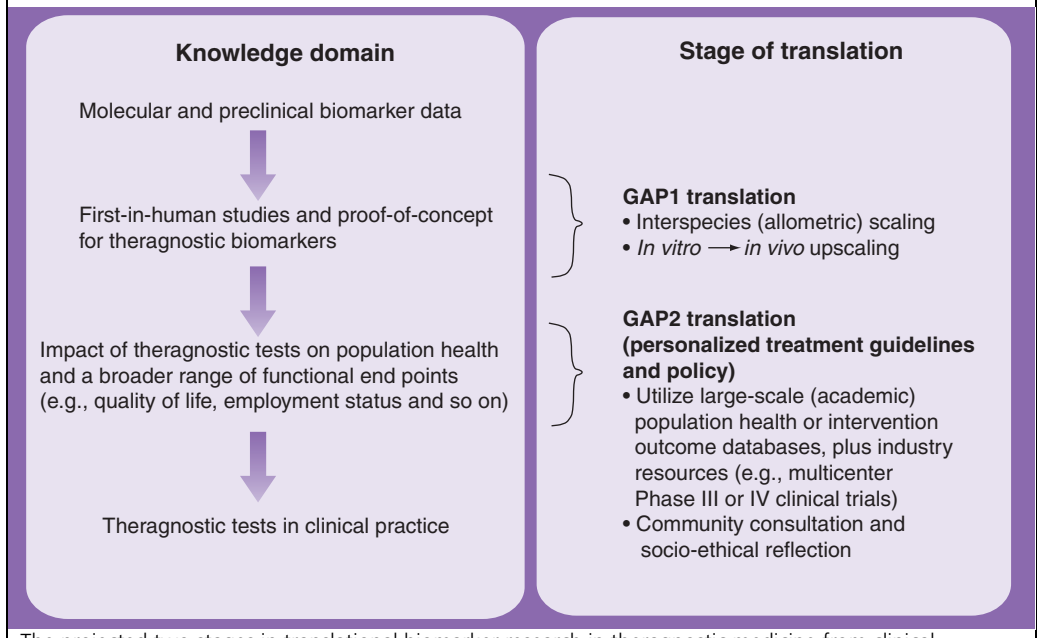
'Unpacking' translational research in theragnostics

GAP1: translation from basic science to first-in-human proof-of-concept

The need for GAP1 translational research in theragnostics stems from three fundamental considerations:

- The obvious interspecies differences in pharmacokinetic pathways and molecular drug targets;
- The inevitable biological contrasts between the inbred laboratory animals with a homogenous genetic background and outbred human populations who exhibit marked genetic variability and exposure to a diverse array of social and environmental factors;
- The need for scaling-up molecular observations *in vitro* to an integrated systems biology context in the whole (human) organism *in vivo* (**Figure 2**).

Figure 2. Stages in translational biomarker research.



The projected two stages in translational biomarker research in theragnostic medicine from clinical proof-of-concept (GAP1) to development of appropriate treatment guidelines based on theragnostic tests (GAP2).

FIH proof-of-concept studies play a pivotal role in bridging the divide (i.e., GAP1) between preclinical biomarker research and large-scale population-based clinical investigations for theragnostic test development and validation. Despite their small sample size and limited scope of inquiry (usually less than 100 subjects per study), FIH studies make an important contribution as a first step in proof-of-concept and knowledge translation between *in vitro* and *in vivo* approaches, or more broadly, in extrapolation of data from animal models to the whole human organism. For example, clinical trials selectively testing patients with certain genetic subtypes of drug targets previously shown to confer an increased likelihood of response can facilitate proof-of-concept decisions on whether and to what extent a new molecular entity (NME) is a viable therapeutic candidate. An inadequate clinical response to an NME in such enriched samples may serve as an early indication of possible therapeutic failure in the general patient population [20].

A glance at leading clinical pharmacology and pharmacogenomics journals attests to the proliferation of genotype–phenotype correlative studies over the past 10 years [21–23]. Many of these studies fall under the GAP1 translational biomarker research; they often have small sample sizes. While contributing to hypothesis generation, studies addressing GAP1 translational research can also lead to false positive or spurious conclusions, particularly in the case of retrospective analyses. In an attempt to develop, implement and disseminate a public genotype–phenotype resource, Stanford University (CA, USA), with funding from the NIH, established the Pharmacogenetics & Pharmacogenomics Knowledgebase (PharmGKB) [102]. This database is part of the NIH Pharmacogenetics Research Network (PGRN), a nationwide collaborative research consortium. The PharmGKB stores data regarding genetic sequence variation and their association with drug-related phenotypes, and provides methods for submission, browsing and download. The PharmGKB is envisioned as an integrated research tool and repository for genetic, genomic, molecular and cellular phenotype data and clinical information on research participants in pharmacogenomics research studies. As of October 9, 2006, the PharmGKB reportedly contained information on 230 genes and variants and 426 drugs. PharmGKB is comprised of clinical and basic pharmacokinetic and pharmacogenomic research data on, but not limited to, the cardiovascular, pulmonary and cancer pathways, and metabolic and transporter domains [102]. These data are publicly accessible on the internet for research purposes. In the short

term, it is conceivable that biomarker data repositories such as PharmGKB will become an important aid to researchers in obtaining clinical proof-of-concept to understand how genetic variation among individuals contributes to differences in reactions to drugs. Looking further, such theragnostic databases may accumulate sufficient 'biomarker–phenotype' correlative studies to be able to inform population-based GAP2 translational research, a pivotal next step in developing theragnostic-guided treatments and health policy (see also section on GAP2).

It is noteworthy that studies aimed at GAP1 knowledge translation can be mistakenly framed as the sole translational research activity on the path from basic biomarker research to individually tailored drug therapy. Although the early phase translational biomarker studies noted above provide preliminary insights into predictive value (e.g., sensitivity/specificity) of theragnostic tests in humans, the complete range of pharmacokinetic and pharmacodynamic variability and attendant predictive performance of theragnostic biomarkers within and among human populations are seldom available at the end of GAP1 translational research. This becomes an acute concern, particularly in the case of theragnostic tests based on genomic, proteomic or other -omic technologies.

An important caveat in pharmacogenomic association studies aimed at personalized medicine is that they exploit the principle of linkage disequilibrium (LD), the co-occurrence of alleles at different genetic loci at a frequency greater or lesser than what would be expected due to random association alone [21,24,25]. Consequently, the genetic loci that are reportedly associated with drug response or toxicity may not necessarily correspond to the causal genetic variants. The degree of LD also varies markedly in different regions of the genome, as well as among different populations [26–28]. Thus, unless the causal genetic variants are ascertained, the informativeness of genetic markers identified in small-scale GAP1 translational research for prediction of drug response will be fraught with uncertainty when therapeutic forecasts are extended more broadly to other populations beyond the immediate study sample [29]. Furthermore, due to the multigenic nature of most human diseases and pharmacological traits, pharmacogenomic biomarkers can be, but are not always, population-specific; divergent sets of genes may influence the clinical phenotypes in different populations [30]. Attention to a large range of social and environmental factors (e.g., smoking, diet or other lifestyle factors) and gene–environment interactions will also be essential to appreciate individual, geographic and population variability in drug effects. Hence, these considerations collectively call for much larger scale population-based GAP2 translational theragnostic biomarker research.

GAP2: translation from clinical proof-of-concept to treatment guidelines based on theragnostic tests

For theragnostic tests and the personalized medicines to become a reality at point of patient care, a broader scope and types of human genetic (e.g., other than single nucleotide polymorphisms), proteomic and metabolomic variation will need to be explained, well beyond what is achievable in small-scale GAP1 translational research studies. This is significant particularly from a clinical standpoint, as noted above, because the only barrier between a patient and severe toxicity or treatment failure will be the theragnostic test itself. In cases where the diagnostic sensitivity/specificity of the test is not sufficiently robust, a number of ethical and legal issues emerge related to knowledge transfer, regulation of novel technologies, commercialization and professional responsibility [10,31,32].

A case in point on the limits of GAP1 translational research is the CYP2D6 drug-metabolizing enzyme that contributes to disposition of several important psychotropic agents. Within the *CYP2D6* gene itself [33], certain alleles are typified by polymorphisms (e.g., insertions/deletions) other than the traditionally investigated common nucleotide substitutions. Attention to rare genetic variants will also be necessary in cases where the test results inform critical decisions on choice of drug prescription or dosage. The required sensitivity and specificity of molecular genetic assays, in a clinical diagnostic context, must be markedly higher than the technical standards acceptable for purely research purposes or biomarker discovery applications. Furthermore, clinicians who are familiar with the rapid turnaround times and relatively low cost of clinical chemistry tests may understandably demand a comparable ease of access, affordability and rapidity of test result (e.g., within several days or ideally by the end of each patient's visit). With the exception of a few specialized research centers and tertiary care centers in developed countries, these 'diagnostic standards' are simply not achievable, or are well beyond the present capacity of public healthcare systems in many countries [11]. Other examples of prospects and limits of GAP1 translational research are available elsewhere [10,34].

GAP2 translational research demands large-scale prospective studies to provide the evidence necessary to change treatment regimens based on diagnostic test results. Another avenue for GAP2 translational theragnostics research, and one that has thus far been overlooked, is the use of population databases such as UK Biobank, the Estonian Genome Project, the Icelandic Healthcare Database and the Quebec CARTaGENE project [17,18,35]. Thus far, the primary focus of these population databases has been the identification of disease susceptibility genes with applications towards drug target discovery or disease risk assessment [17,36]. Conceivably, these biological and phenotypic/epidemiologic repositories can also contribute to the identification of theragnostic tests to individualize drug treatment regimens. Potential benefits of population biobanks, and the means or research methodologies to achieve them over the long term, still remain ill-defined. The data contained in biobanks are quite variable in terms of content and quality, as well as the type of consent obtained from participating subjects. There is little harmonization or standardization of data collection and banking procedures amongst biobanks [103], making the exchange and sharing of data practically and financially difficult, a situation further compounded by common professional tendencies in biomedicine and human genetics research towards data withholding [16,35,37,38]. It would be timely to initiate key stakeholder meetings and wider community consultations to examine the impact of biobanks and theragnostic testing on medical practice, health professionals' education, awareness, professional responsibilities and how best to communicate and translate findings related to new theragnostic markers identified or validated in biobanks.

It is still unclear whether the dual objectives of biomarker validation for disease susceptibility and drug response variation are both achievable within the constraints of a single population biobank. For instance, disease phenotypes can be ascertained dichotomously as 'present' or 'absent'. In contrast, for drug response phenotypes to be clinically meaningful, they may require a higher resolution definition with continuous measures and repeated observations over time. Drug response may also fluctuate due to drug–drug interactions or time-dependent changes in physiological states (e.g., diurnal rhythms or menstrual cycle). Another more focused application of population biobanks could be the identification of gene–environment interactions in the context of drug therapy. Populations of patients who are tracked for their drug response over long periods of time can help to discover and validate rare but serious drug side effects during postmarketing safety assessments. Consider, for example, the relatively uncommon but lethal cardiac side effects of the selective cyclooxygenase 2 (COX-2) inhibitor rofecoxib (Vioxx®) that could not be detected reliably in small-scale early phase premarketing clinical trials. However, given the global nature of contemporary bioscience research, drug development and marketing of new medicines, it is very likely that a coordinated multi-biobank approach to theragnostic applications will be necessary.

Technical, bioinformatic and phenomic integration in theragnostics: rationale for centralized translational clinical research centers

Success in translational theragnostic research depends on expertise in three fundamental domains:

- Core technical expertise to generate high-throughput biomarker data;
- Collection of large volumes of phenotypic data from patients treated with drugs;
- Ability to perform correlative bioinformatics analyses between biomarker data and drug-related phenotypes.

Due to the rapidly declining cost of genotyping and other biomarker genotypic technologies, availability of phenotypic data is now the most crucial and rate-limiting step among these three domains [38,39]. This creates a statistical conundrum: in order to attain adequate statistical power to allow correction for multiple testing and association analyses among multiple biomarkers and clinical end points, researchers require an increasingly larger number of human subjects or biological specimens (e.g., tumor biopsy material) to accompany the high-throughput theragnostic biomarker data [38,40]. Therefore, in addition to the technical integration, there is an acute need to establish local, national and international 'phenomic' databases that can integrate drug-related phenotypes across a broad range of treatment outcomes in different therapeutic areas, using both public and privately-sponsored pharmaceutical research and clinical trial data (a significant challenge given the proprietary, and thus secret, nature of such data).

To the extent that integration across technical (e.g., amongst genomic–proteomic–metabolomic divides) and phenotypic dimensions is an emerging and timely theme in translational theragnostic research, what are some of the optimal

research strategies that can deliver on this goal? We submit that one of the internationally recognized integrated models for translational clinical research is the General Clinical Research Centers (GCRCs), a national US network of approximately 78 centers, mostly located within the research hospitals of academic medical centers. The primary mission of the GCRCs is to provide a research infrastructure for clinically oriented investigators. Furthermore, GCRCs act as an important link between molecular research and clinical practice, allowing investigators to translate knowledge gained through basic research into the development of new or improved diagnostics and therapeutics for patient care. With the emergence of theragnostics and increasing public demands for personalized medicine, it would be timely to amend the existing GCRC research infrastructure to accommodate integrated biomarker research towards the eventual goal of individually-tailored drug therapy. Conceivably, theragnostic-oriented GCRC networks can also serve to pool phenotypic information derived from industry-sponsored clinical trials (assuming stricter requirements for data disclosure) along with publicly-funded academic pharmaceutical research across medical disciplines both at institutional, national and international levels.

Recently, the US NIH created a national consortium to transform how clinical and translational research is conducted, ultimately enabling researchers to provide new treatments more efficiently and quickly to patients. This new consortium, funded through Clinical and Translational Science Awards (CTSAs), aims to link about 60 institutions by 2012 in order to revitalize clinical and translational science [104].

Expert commentary & future outlook

From antiquity to the present day, there has been tension between theoretical and practical work [41]. The ancient Greeks, for example, valued theory (theoria) over applied inquiries [42], while Enlightenment scholars continued to make such distinctions. According to Cohen [43], the notion of 'pure/basic research' was developed in 1648 by philosophers to differentiate science and natural philosophy (dealing with abstract inquiries) from disciplines concerned with concrete notions or applied subject matters. This disctinction has also contributed to a now commonly accepted 'linear model of innovation' [41] in science, such that innovation starts with basic [molecular] research, followed by applied [translational] research and development, ultimately culminating in a complex process of industrialization, high-throughput manufacturing, economic development and dissemination of resulting goods to benefit civil society and attendant industries.

In this article, we challenge this linear model of scientific progress in the context of the development of clinically relevant molecular markers. We demonstrate that the 'middle section' of this process, now commonly referred to as translational research, is far more complicated, and is actually comprised of two very different gaps, herein called GAP1 and GAP2 research. We submit that adequate recognition or differentiation of these two very different types of translational research (e.g., in terms of research goals, scale and motivations) is essential to ensure continued progress towards personalized therapeutics and development of appropriate health policies (**Figure 2**). Notably, 'reverse translational research' is also plausible in the event of unexpected clinical observations (e.g., drug toxicity or treatment resistance), and can be an important trigger for fundamental basic research. Ultimately, we suggest that basic and applied clinical research complement each other, and are essential for resolution of the challenging questions faced in pharmacological research and application at point of patient care. Thus, debates about the relative importance of either type of research are counter productive, because they create artificial and unnecessary divides between equally important forms of scientific inquiry.

Personalized drug therapy is not a new concept [25,44–46]. However, theragnostic testing is beginning to transform medical practice in a fundamental manner by placing a greater emphasis on the notion of probability [47,48], instead of traditional expectations about definitive prediction of treatment outcomes. The scope of research in this field has changed over the past several years with the availability of new technical and methodological approaches, such as proteomics and metabolomics. At the moment, these promising technologies are best suited for exploratory research and remain to be validated both in terms of sensitivity/specificity of the data they generate and their mechanistic relevance in explaining variability in treatment outcomes in a population context. In parallel to these new technologies, the precision of existing technologies in applied genomics (i.e., high-throughput genotyping and gene-expression analysis) has increased while the unit cost of assays has markedly decreased.

Arguably, all these technical advances reflect an emerging 'engineering triumph' in biomarker research and, more broadly, in diagnostic

medicine [49]. However, for this to translate into a 'biological triumph' in a clinically meaningful manner, there is an acute need for the integration of biomarker data. Our fear is that continued reliance on a singular biomarker technology platform by different stakeholders may result in an artificial compartmentalization (or fragmentation) of biomarker research. For example, human geneticists and pharmacogenomics researchers may favor genotyping and gene-expression analyses, while biochemists may primarily utilize proteomic methods. On the other hand, drug effects are determined multifactorially, and the human genome is subject to poorly understood plasticity. Thus, an integrated and indiscriminate approach to biomarker technology platforms – whether they rely on genomic, proteomic and/or other methodologies – should be adopted, so long as it explains individual differences in drug efficacy and safety in a mechanistic and clinically meaningful manner. It is against this need for technical and phenotypic integration that the new subspecialty of theragnostics and the attendant requirement for translational research centers are emerging.

Despite considerable efforts in GAP1 translational biomarker research, there remains a large and serious gap in further translation of biomarker data obtained in FIH pharmacogenomic proof-of-concept studies to a population level for the development of personalized treatment guidelines using genetic or other types of theragnostic tests. Large-scale biobanks are being developed in several countries around the world to meet these objectives. These databases concern the general population as opposed to particular patient groups or families. The amount of information gathered on the individual, as well as the types of diseases studied, constitute a divergence from the genetic registers of the past as well as from the gene-hunting (or discovery) research of today. Another change in the research paradigm is the desire for public consultation. These databases depend on public participation and assent. Therefore, it is important to encourage a free, open and useful dialogue among all stakeholders involved.

The accumulation of high-quality data in biobanks that meets minimal standards for utilization in downstream clinically relevant analyses is critical for translational research. Databases containing poor-quality or incomplete information can lead to misleading conclusions in meta-analyses that will not hold up to the test of time. Moreover, serious challenges arise in harmonizing divergent database information; without robust quality control metrics, translational research can lead to errors being generated during data transfer, pooling and bioinformatics analysis.

Due to the inherent focus on theragnostic 'product development', whether it be in biobanks or GAP1 translational research, there may be cause for concern over how much weight will be given to more fundamental research that may not directly have an application in the clinic [38]. Such concerns coincide with a shift in the perceived mission of academe and medical research, particularly with regards to the applied sciences. In addition to being sites of advanced teaching and research (the university's 'first' and 'second' missions), universities must now engage in knowledge transfer that leads to technology development and economic growth (the 'third mission'), a role that has proven popular with governments, industries and universities worldwide [3]. To facilitate this third mission (and some would argue, to transform universities into 'entrepreneurial' institutions), laws and policies have been implemented to ensure strong protection of intellectual property rights and facilitate commercialization and technology transfer. Such protection can have serious negative consequences for the conduct of academic research and free sharing of data amongst population biobanks [6,38].

Advances in theragnostics will likely take place in small but significant steps. Development of the necessary research resources – i.e., interdisciplinary research centers, harmonized large-scale biobanks, and so on – to enable the integration of molecular biomarker data with the attendant environmental factors, and the subsequent translation into clinical practice and regulatory frameworks, needs to be planned much sooner [50,51]. There is a clear need for translational clinical research centers that can integrate the full range of biomarker data from different levels of the biology and technology platforms (e.g., genomic, proteomic and metabolomic) as well as a broad range of pharmacological phenotypes (i.e., phenomics) in a way that is meaningful from both the physicians' and patients' individual perspectives [16,30,52,53].

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Highlights

- In the context of personalized therapeutics and theragnostics, translational research is clearly a complex, multistage and nonlinear process. There is a large divide between molecular findings and their clinical applications, and between what we know and what we practice. This calls for a more effective translation of basic research into clinical practice.
- Inadequate recognition of two major bottlenecks impedes the translation of current theragnostics research to the point of patient care: translation from basic science to first-in-human proof-of-concept; and translation from clinical proof-of-concept to development of evidence-based personalized treatment guidelines.
- The need to harmonize large-scale population biobanks to enable translation of theragnostics research is fraught with scientific, technical, social and political challenges. However, these challenges are not insurmountable.
- There is a desperate need for coherent standards in biobank management that will enable the development of the databases and relational database interactions that can facilitate the translation of information into personalized therapeutics. Current databases require substantial effort to transform data into the appropriate formats for analysis. In addition, without quality control metrics in place, translational research can lead to errors being generated during data transfer, pooling and bioinformatics analysis.
- Broad public and stakeholder engagement is essential for the development of effective and socially acceptable biobanks that can allow a deeper understanding of both disease pathophysiology and individual determinants of variability in drug response and toxicity.
- The application of theragnostics at the point of patient care, i.e., the dream of personalized medicines, requires broad scale interdisciplinary collaboration along the development pathway, from rigorous basic and applied -omics research to the ethical implementation and delivery of safe and effective therapeutics.
- There is an acute need for resource development, for example, translational clinical research centers, for integration of biomarker data from different levels of the biology and technology platforms, as well as a broad range of pharmacological phenotypes in a way that is meaningful from both the physicians' and patients' individual perspectives.

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