In 1990, an international effort was launched to coordinate the mapping of the human genome and with it, the opportunity to understand the unique self at the most fundamental level. In the year 2000, on the completion of the first survey of the entire Human Genome Project, past US President Bill Clinton declared that the project would “revolutionize the diagnosis, prevention and treatment of most, if not all, human diseases.” Furthermore, Clinton recognized in his remarks that “some forms of leukemia and breast cancer already are being treated in clinical trials with sophisticated new drugs that precisely target the faulty genes and cancer cells, with little or no risk to healthy cells.”

The Precision Medicine Initiative, announced by US President Barack Obama in his 2015 State of the Union Address, was the next major federally-funded effort to fulfill the potential of a detailed map of the human genome. Advances in bioinformatics and scalable gene sequencing have paved the way for the current era of individualized medicine, in which researchers, providers, and patients work together to develop a more precise approach to diagnosis and treatment. In the National Institutes of Health (NIH) definition, “Precision medicine is an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person.” The NIH is developing a one million subject cohort as part of the initiative; in which full genetic sequence data, together with clinical and biomarker profiles, will allow for the assessment of the interaction between genotype and phenotype over time, enabling the development of tailored disease prevention and treatment approaches. President Obama highlighted the treatment of cystic fibrosis (CF) as an example: “I want the country that eliminated polio and mapped the human genome to lead a new era of medicine: one that delivers the right treatment at the right time. In some patients with cystic fibrosis, this approach has reversed a disease once thought unstoppable.”

In 2015, 13 of the 45 drugs approved by FDA were characterized as precision medicines by the Personalized Medicine Coalition (PMC). These approvals continue a trend that began in 2014 when nine out of 41 new drugs were classified as precision medicines. In its evaluation of new drug approvals, the PMC defined them as those therapeutic products for which the label included a reference to specific biomarkers that qualified individual patients for therapy. In addition to the 13 drugs approved in 2015, FDA approved new indications for previously existing drugs narrowing their intended use to subpopulations of patients who could be identified as more clearly benefiting from the treatment.
This year, the Obama Administration is launching the National Cancer Moonshot, a $1 billion initiative to provide the funding necessary for researchers to accelerate the development of new cancer detection and treatments. These efforts will include cancer-related research at the NIH, the FDA, and the Departments of Defense and Veterans’ Affairs, and is expected to be another example of scientists, cancer physicians, advocates, philanthropic organizations, and representatives of the biotechnology and pharmaceutical industry working together to focus on major new innovations in the understanding of and treatment for cancer.

From the drug development point of view, incorporating the concepts of precision medicine early in the drug development cycle is important, both to set the stage for success in later phase drug development, and for delivering optimal therapeutics to individual patients. The current paradigm of drug development frequently includes initial safety and pharmacokinetics testing in healthy subjects in Phase I studies, followed by efficacy and dose-ranging studies in patients with the disease of interest. In some therapeutic areas, particularly in oncology, this approach is transitioning to a precision-guided approach with earlier targeting of patients who may uniquely benefit from a therapy. We consider the implications of this paradigm shift on the drug development cycle and the factors that influence the transition from traditional drug development to a precision medicine approach.

**The path from traditional to precision medicine starts in early clinical development**

Historically, most novel therapeutics have been developed without a full understanding of the molecular mechanism of the disease and the treatment. A transition to precision-medicine based strategies of drug development is made possible by a greater understanding of the molecular basis of health and disease, the proliferation of “-omics”, vast advances in technology, and innovative methods that enable to characterize the heterogeneity in human populations at the molecular level.

To make this transition, there needs to be a paradigm shift across multiple drug development stages, most notably in early drug development. Early stages of development comprise clinical and pre-clinical studies and supporting research activities such as toxicology, chemistry, manufacturing, and control (CMC), development of analytics and diagnostic tools, that culminate with the compound achieving proof of concept (POC).

Typically, new drugs enter early clinical development with a strategy that defines a set of clinical studies, including their high-level designs, and other supporting research activities to be performed. Many drug development programs advance to clinical testing with at least one defined tailoring hypothesis. As concepts of precision medicine become increasingly widespread in the scientific community, these programs face key strategic alternatives, each with different implications and difficult tradeoffs that differ from the traditional development paradigm. These alternatives depend on the point in time when a specific tailoring hypothesis becomes the main focus of the development program. At one extreme, a traditional (Broad/Exploratory) development paradigm starts with the clinical evaluation of a broad population, to gather information that may allow for identification of potential tailoring hypotheses later in development. On the other extreme, the development path could commence with a singular tailoring hypothesis in a narrowly defined patient population (Narrow/Focused). In between these two extremes, a myriad of possibilities for development choices exist along the development continuum. In particular, the ends of the spectrum of development strategies translate into radically different choices for early clinical development (Table 1).

**Broad/Exploratory** strategies start with a largely agnostic view of the ultimate tailoring approach and intend to prove the therapeutic concept by enrolling heterogeneous patient populations in the early clinical trials. Taking advantage of this diversity, Phase 1 trials may yield unexpected insights that can be further explored with flexible or adaptive trial designs. As the molecules progress to Phase 2, studies become larger and more complex, due to the necessarily lower signal-to-noise ratio observable in an early broad population. Failure to prove the therapeutic concept in the general population is likely to result in termination of the drug. Alternatively, the drug response may subsequently be explored in a further refined subpopulation. These further explorations can begin at the POC study, with the potential of extending to more focused studies in other subpopulations, which can be either identified at the POC stage or defined based on a strong scientific theory.

**Narrow/Focused** strategies, in contrast, start with a strong predisposition towards a single-or a select few- tailoring hypotheses, upon which the proof of the therapeutic concept is focused. Typically, the probability of success is the highest for these tailoring hypotheses, and positive proof of the hypotheses is a prerequisite for the continued development of the program. Once proven successful, the program can continue on this tailored path, as well as potentially expand into other subpopulations and/or broader populations. In the Narrow/Focused paradigm, the initial studies are typically smaller, due to the expectation of a higher drug effect size. However, they also present operational challenges for subject recruitment, given the demand for a more stringently defined patient population, rather than a healthy subject population. Indeed, the first study in humans may also serve as the POC study in this paradigm, which differs from the traditional drug development approach in which the POC study is usually preceded by single dose and multiple dose safety/pharmacokinetics studies. Furthermore, the exploration of alternative tailoring hypotheses is typically avoided in the focused strategy approach.
### Development Strategy

<table>
<thead>
<tr>
<th></th>
<th>Broad/Exploratory</th>
<th>Narrow/Focused</th>
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</thead>
<tbody>
<tr>
<td><strong>Hypothesis testing</strong></td>
<td><strong>Broad</strong>&lt;br&gt;Wide exploration of tailoring hypothesis</td>
<td><strong>Specific</strong>&lt;br&gt;Pre-defined tailoring hypothesis at the core</td>
</tr>
<tr>
<td><strong>Disease Population</strong></td>
<td><strong>Extensive</strong>&lt;br&gt;Heterogeneous population to built efficacy hypothesis</td>
<td><strong>Narrow</strong>&lt;br&gt;Homogeneous sub-group focus to confirm efficacy hypothesis</td>
</tr>
<tr>
<td><strong>Phase I Safety Study Population</strong></td>
<td><strong>Typically Healthy Subjects</strong>&lt;br&gt;Understand safety in heterogeneous population</td>
<td><strong>Target Patient Population</strong>&lt;br&gt;Safety in targeted population most applicable</td>
</tr>
<tr>
<td><strong>Disease Markers</strong></td>
<td><strong>Search and Find</strong>&lt;br&gt;Evaluate many biomarkers, find those that respond</td>
<td><strong>Refine and Confirm</strong>&lt;br&gt;Select a few, specific prognostic and predictive biomarkers</td>
</tr>
<tr>
<td><strong>Strategic Tailoring Decision</strong></td>
<td><strong>Post-PoC</strong>&lt;br&gt;Decision as late as Phase II/III; triggers companion diagnostic</td>
<td><strong>Early</strong>&lt;br&gt;Build decision and companion diagnostic into early development</td>
</tr>
<tr>
<td><strong>Study Designs</strong></td>
<td><strong>Adaptive Characteristics</strong>&lt;br&gt;Explore breadth and adapt as information is acquired</td>
<td><strong>Fixed Study Design</strong>&lt;br&gt;Greater initial information allows for a more defined design</td>
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The challenge, thus, is having enough relevant information to confidently choose a tailoring hypothesis early in drug development.

#### Implications of data and decisions along the development strategy continuum

Throughout the development of a drug, making the choices between the two extremes of the competing early development strategies results in significant downstream implications (Table 1, Figure 1). The decision tree in Figure 1 depicts a simplified view of the tradeoffs a development team must consider based on the available information. The primary decision is between the development of: 1) a broadly applicable drug potentially benefiting a large population, with an associated greater market potential or 2) a drug with a narrow patient population, albeit with a higher effect size and probability of technical success.

The reality of drug development is quite complex, and there is a continuum of options within the extremes depicted in Figure 1. A development path that starts broadly can end up with a narrowly defined subpopulation, by a midstream shift to a more tailored approach based on emerging and prior evidence. Similarly, a path that starts narrow does not preclude a population expansion that can end up with broader applicability and a larger ultimate target population, as new information is gathered from both clinical trials and from the extended scientific community. However, the choice of starting strategy does indeed have differing implications, and it is important to properly frame those implications in order to choose the most appropriate strategy for the compound. A formal analysis of the resources and time necessary to reach the nodes in the decision tree, including the probabilities for each branch, and a probability-weighted overall outcome based on the tenets of decision sciences, can be performed to inform and improve development choices. This information can subsequently be used to contrast the expected cost and duration for competing strategies and thus facilitate better decision making. Such assessments are dependent on the applied designs of the studies, as well as the knowledge base of the novel therapeutic, the disease state, the target and the strength of the tailoring hypothesis.

An example of the Broad/Exploratory approach is Eli Lilly’s evaluation of a new compound in a proof of concept trial. An evaluation of multiple biomarkers -at baseline and over
time- was built into the study design, as an attempt to identify higher responding subpopulations based on the underlying pathogenesis. However, the sample size and randomization algorithm were not designed to ensure adequate power for any specific tailoring hypothesis. Although several biomarker trends were observed, they were not compelling enough to continue the program. The limitation of this approach is that only subpopulations with a substantial effect size have the potential to be identified. Hence, as in this example, when the data for the primary objective are not sufficient to support continued development in the broad population, investment in additional exploration of subpopulations is also highly unlikely unless a very strong and compelling signal is observed. In this case, the scenario that unraveled is similar to branch D in the decision tree (Figure 1).

The broad strategy can move a drug with wide applicability to later stages of development, yet maintains an opportunity for finding benefit in a drug that fails the broad hypothesis, if an alternative tailoring hypothesis is identified and subsequently proven during early development. The implied risk is that of failing to identify a key subpopulation due to inadequate representation in the early studies, and the risk of a delayed, and therefore more expensive, failure (if the drug truly does not work) due to sequential POC studies in two or more different subpopulations.

Choosing the narrow strategy for early development has different implications. In this focused approach, a drug may show clinical benefit in the initial targeted patient population, supporting continued development in this paradigm. Furthermore, the option to continue to evaluate in a broader and/or other defined subpopulations, which will require additional investment, is maintained. One drawback to the narrow strategy is that the burden of proof at the initial stage is higher than for the traditional approach. Additionally,

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**Figure 1.** A decision tree depicting selected broad versus focused drug development strategies. Multiple strategies can be adopted for a new drug candidate as it enters clinical development, and each of these strategies results in unique late phase implications. Many hybrid strategies can be envisioned.
These choices can have a significant impact and the tools to be used for that purpose. Information to identify the right population, is important to define the most relevant at the start of each development program, it test the precision medicine hypothesis. At and to influence the study design to directly study a more focused patient population, relevant; stronger “tailoring” evidence allows to include in the POC studies is extremely result in a precision medicine. (branches F and G) and would ultimately favors the narrow and focused strategy of disease and response is sparse, and there are many competing tailoring hypotheses, the ultimately successful drug is likely to journey through different branches of the decision tree (e.g., branches A,B, E,F or G) than the drug that ultimately fails (e.g., branches C, D, or H). In both cases, the broad strategy would be a better fit for the drug, as it has a shorter path to success and lower risk of unjustified failure (branch H). On the other hand, information in support of a narrow and specific subpopulation with clearly defined biomarkers (e.g., genetic polymorphisms) favors the narrow and focused strategy (branches F and G) and would ultimately result in a precision medicine.

The choice of the most appropriate population to include in the POC studies is extremely relevant; stronger “tailoring” evidence allows to study a more focused patient population, and to influence the study design to directly test the precision medicine hypothesis. At the start of each development program, it is important to define the most relevant information to identify the right population, and the tools to be used for that purpose. These choices can have a significant impact on different label indications, such as in the example of ivacaftor mentioned above. Other considerations when making drug development choices are the impact on operational efficiency at the trial level/program level and the impact on program costs and length, when companion diagnostics are required. At the enterprise level, portfolios need to balance their cost, quality, and operational efficiency. Including a large proportion (20%) of Phase 1-3 trials with a focus on precision medicines in the portfolio, significantly reduced the overall operational efficiency. The same effect was observed when a higher percentage of a portfolio consisted of patients with rare versus “traditional” diseases. However, there may be justification for these choices through benefits in value or attrition. Thus, these factors, together with the regulatory environment, need to be taken carefully into account when development options are considered.

Complexities along the journey towards a Precision Medicine approach

Advances in technology have yielded enormous repositories of information, as the sequence of entire individual genomes can be catalogued and queried, and have been instrumental in improving the understanding of the molecular mechanisms defining health and disease. Adding more precision to medicine requires a continued collaborative effort between the discovery engines of academics, national institutions, industry, and health care organizations, in order to better systematize and organize this plethora of information for optimal application in drug development. This is crucial for growing the understanding of the heterogeneity and complexity of drug responses, diseases, and patient populations. The objective of Precision Medicine is to link information, such as the phenotypic and genotypic data available from the Human Genome project, to therapeutic information which will benefit the patient. The abundance of available data leads to technology and privacy concerns, together with the difficulty to adequately interpret the information. Thus, flexibility is paramount to be able to adapt the development approach as new data is received. Because every drug and target is different, and because information is available in stages, Bayesian methodologies, where new information is used to refine or change the approach in development, should be considered. This approach can also maximize the use of real-time data obtained via technological advances; which will in turn improve and accelerate the way in which prescribers and patients are able to modify dosing regimens, adapting them to their specific needs.

The strength of the data to be used in a tailoring approach ultimately affects the strategy chosen for the development of a given drug. The decision tree depicted in Figure 1 merely outlines the strategic conundrum that is typical in early development planning; many permutations or hybrid strategies can be devised for a novel therapeutic in development. In other words, the strategy may represent a continuum of choices across the individual decisions depicted in Table 1. Despite present challenges for progressing to a more focused or tailored approach, almost 30% of drugs approved in 2015 were precision medicines. The US Administration’s continued commitment to accelerating medical research is exemplified by the Precision Medicine Initiative in 2015 and the new National Cancer Moonshot in 2016.

The ultimate goal is to benefit the patients; the question is how to make it more widespread – and whether precision medicine is appropriate in all cases.
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