Personalized Medicine: Trends in Clinical Studies Based on National Registry Data

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ABSTRACT

OBJECTIVES: Targeted therapies using pharmacogenomic data promise to improve the safety, efficacy, and cost-effectiveness of drug treatment significantly. To assess research progress in targeting biopharmaceutical interventions to address unmet medical need, we investigated therapeutic, temporal, and economic trends in personalized medicine using data from a national clinical trial registry.

METHODS: Personalized medicine (PM) is the use of a patient's genotype or other molecular diagnostic (pharmacogenomic) data to guide a treatment decision. We queried ClinicalTrials.gov for studies using pharmacogenomic criteria for inclusion or exclusion, or for stratifying outcomes, restricting our analysis to Phase III or IV studies initiated on or before January 7, 2009. We verified the sensitivity of our search strategy using a known set of studies for which PM-related trials have been conducted.

RESULTS: 1.7% (N=155) of registered Phase III/IV trials in the US (N=9,111) used pharmacogenomic data. Over time, the number of trials using pharmacogenomic data has increased greatly and, as expected, most PM trials (55%) were in the therapeutic areas of oncology and hematology. However, we observed a marked increase in the number of PM trials for drugs targeting disorders with highly variable treatment response, such as neurology and mental health disorders including Alzheimer's, depression, and schizophrenia. In addition, we found that the source of funding for PM trials increasingly comes from the pharmaceutical industry rather than from public sources.

CONCLUSION: Targeting drugs to smaller subgroups is assumed to result in treating those patients most likely to respond and least likely to experience an adverse event. These data are consistent with the idea that these gains will be experienced broadly across therapeutic areas, however, the degree of impact will vary according to our understanding of the molecular basis of disease, with associated implications for assessing relative clinical and cost effectiveness.

OBJECTIVE

- In order to assess research progress in targeting biopharmaceutical interventions to address unmet medical need, we investigated therapeutic, temporal, and economic trends in personalized medicine using data from a national clinical trial registry.

BACKGROUND

- Personalized or stratified medicine is the use of a patient's genotype or other molecular diagnostic (pharmacogenomic) data to guide a treatment decision.[1]
- Personalized medicine is believed to hold the greatest promise in therapeutic areas such as oncology where the patient-to-patient variability in response to treatment is particularly high (among other factors).[2]
- The rapidly falling cost and broad availability of DNA sequence data is a key technological driver of PM.
- Recent policy changes by major health insurers (payers) have emphasized the importance of PM diagnostic tests in treatment selection.[3,4]
- However, the commercial impact of PM has so far been modest, with relatively few examples accounting for a small share of the overall market for pharmaceuticals. Aside from the modest number of PM drugs on the market, there is very little available information on the evolution of PM and the near term potential impact of PM on clinical development and practice.

METHODS

Data Source

- ClinicalTrials.gov, a registry of federally and privately supported clinical trials conducted in the United States and around the world.
- Time period covered: July 1993–December 2008.

Study Design

- ClinicalTrials.gov was queried for studies using pharmacogenomic criteria for inclusion or exclusion, or for stratifying outcomes.
- Analysis was restricted to Phase III or IV studies initiated on or before January 7, 2009 and conducted in the United States.
- Search terms were compiled from pharmacogenomic literature.
- The list of search terms (and associated phrases) included: biologic marker (biomarker, markers, signature molecule), overexpression (overexpress), overexpressing, expression (expressed), expressing, mutation (DNA alteration, gene alteration, genetic alteration, genetic chance, molpath.mut, mutated, mutations, sequence alteration), genotype (genotyping), receptor, genetic, express, and snp (single nucleotide polymorphism, snp info).
- Sensitivity of the search strategy was validated using a known set of breast cancer studies for which PM-related trials have been conducted.

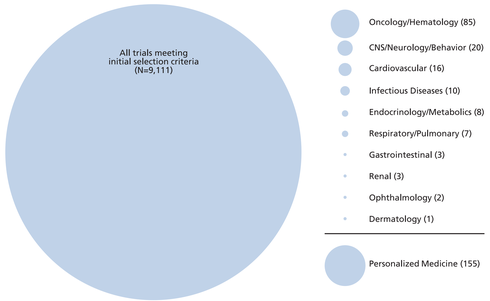
Statistical Analysis

- Results were categorized by therapeutic area, stratification marker, inclusion/outcome criteria, and safety/response endpoints.
- Simple descriptive statistics were used to identify therapeutic, economic, temporal, and trial characteristic trends.
- Trends in PM over time were analyzed using the start year of each clinical trial (see Figures 2, 3, and 5).

RESULTS

Figure 1: Identification of Relevant Trials

- We identified 9,111 Ph III or Ph IV trials that met the initial inclusion criteria.
- Of these, 155 (1.7%) were identified as PM-related.



RESULTS (CONT.)

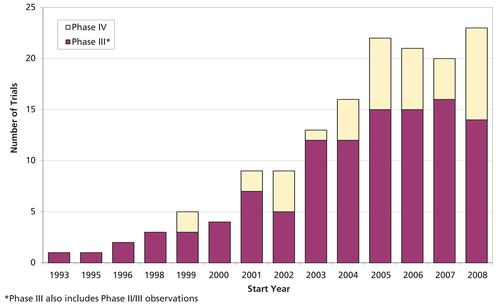
Table 1: Number of PM Clinical Trials by Condition and Therapeutic Area

- Among the identified trials, a few conditions represented the majority of those observed in CNS/neurology/behavioral, and oncology/hematology therapeutic areas. PM-related trials for depression or schizophrenia, and breast cancer were most prevalent within their respective therapeutic areas.

Therapy Area	Condition	Number of Trials N	%
Cardiovascular	Coronary Disease/Dyslipidemia	6	4%
	Familial Hypercholesterolemia	7	5%
	Other	3	2%
CNS/Neurology/Behavior	Addiction	5	3%
	Alzheimer's Disease	4	3%
	Depression/Schizophrenia	8	5%
	Other	3	2%
Dermatology	Cutaneous Sarcoidosis	1	1%
Endocrinology/ Metabolics	Pompe Disease	2	1%
	Other	6	4%
Gastrointestinal	Gastrointestinal	3	2%
Infectious Diseases	Hepatitis	3	2%
	HIV	4	3%
	Other	3	2%
Oncology/Hematology	Breast Cancer	48	31%
	Colorectal Cancer	4	3%
	Haemophilia	3	2%
	Lung Cancer	7	5%
	Prostate Cancer	3	2%
	Other	20	13%
Ophthalmology	Macular Degeneration	2	1%
Renal	Renal Disease	3	2%
Respiratory/Pulmonary	Asthma	7	5%
Total		**155**	**100%**

Figure 2: Number of PM Clinical Trials by Phase and Year

- Initial PM research concentrated heavily on Phase III studies. Since 2001, however, there has been a marked increase in the number of Phase IV trials that use pharmacogenomic data: From 2001 to 2008, the number of Phase IV trials initiated grew at an annual rate of 44%. During the same period, the number of all trials initiated (Phases III and IV) grew at 19%.



*Phase III also includes Phase II/III observations

RESULTS (CONT.)

Figure 3: Distribution of PM Clinical Trials by Therapeutic Area and Growth Over Time

- Given the progress in understanding the molecular biology of cancer over the last several decades, not surprisingly, we found PM approaches exclusively in oncology and hematology up until 1999. From 2002 to 2008, however, there was a notable increase in the number of PM trials for cardiovascular and neurological/behavior conditions. Disorders with highly variable treatment response, including Alzheimer's disease, depression, and schizophrenia, have increasingly become a focus of PM.

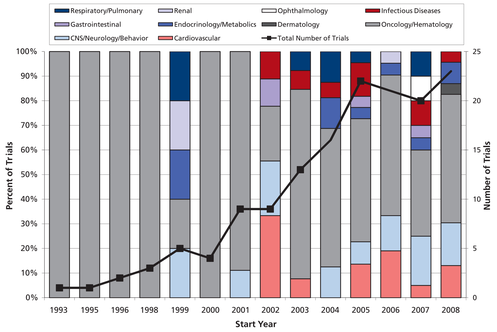
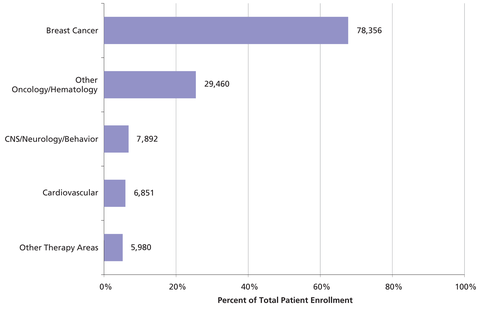


Figure 4: Patient Enrollment in PM Trials by Therapeutic Area

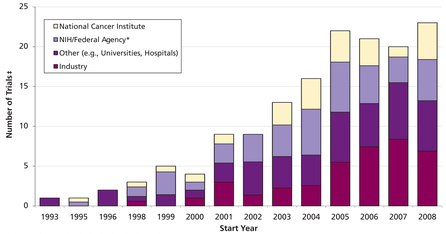
- By far, breast cancer PM trials saw the largest patient enrollment. Oncology, neurology, and cardiovascular trials together accounted for 95% of all patient enrollment over the time period studied.



RESULTS (CONT.)

Figure 5: Number of PM Clinical Trials by Funding Source and Year

- The mix of funding sources for PM trials has grown more diverse, with the share of PM trials funded by the pharmaceutical industry increasing from about 15% in 2002–2003 to more than 35% in 2007–2008.



* Federal agencies include the FDA, CDC, and VA
‡ Some trials list multiple funding sources

DISCUSSION/LIMITATIONS

- Growth in the number of Phase III PM trials appeared to level off after 2003, while the number of Phase IV trials continued to increase (see Figure 2). This increase over time suggests that products already on the market may become subject to additional PM testing. It may also reflect the value of retrospective studies to investigate differential efficacy or safety, whether sponsored by pharmaceutical industry or other funding sources.
- Sensitivity of search terms was only tested in an oncology setting; key terms from other therapeutic areas may have been omitted.
- Registration on ClinicalTrials.gov is not compulsory for privately-funded trials, therefore the proportion of privately-funded studies may be underestimated.
- Trends are not adjusted for the total number of trials registered each year (period and cohort trends may be misrepresented).

CONCLUSIONS

- Data were consistent with the idea that in the future gains from PM will be experienced more broadly across therapeutic areas, with underlying demand a function of several factors including variability in treatment response and unmet need.
- Advances in clinical development of PM appears to also follow advances in the scientific understanding of the molecular basis of disease, with potential implications for assessing relative clinical and cost effectiveness.
- Research into personalized medicine will continue to gain importance to payers, particularly in areas with high-cost specialty therapeutics, and also as the cost for genetic testing and other sophisticated diagnostic methods continues to fall.

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