

Enabling Personalized Medicine November 2007 Update

Personalized Medicine – the next phase of the digital wave

“We’ve identified Personalized Health Care as one of the top priorities at HHS... Personalized Health Care is about opportunities that we’ve never had before. Our job is to seize these opportunities, and to turn them squarely to the benefit of individual patients. When we do that, we’re improving care for every patient, and we’ll improve the value in health care generally.” Michael Leavitt, US Secretary of Health & Human Services¹.

- Healthcare is the latest industry to be transformed by the digital wave.
- The digital wave is empowering Personalized Medicine and catalyzing change.
- Personalized Medicine delivers efficient solutions to many of the major problems that need to be addressed by the Healthcare industry.
- Insights from the wave’s previous impacts have relevance to Healthcare and provide confidence that Personalized Medicine can deliver meaningful change.
- BrainResource is delivering Personalized Medicine solutions today as well as having a development program for future solutions.

This industry thematic aims to provide an update of the evolution of Personalized Medicine and context for BrainResource’s strategic positioning. For those interested in our scientific outcomes, please see a recent invited position paper on Personalized Medicine by Dr Evian Gordon² and the many publications listed on our website.

Background: BrainResource provides information to empower users to make better choices in Healthcare (WellBeing and Disability). Our focus is on brain Marker discovery using our unique standardized methodology and large scale integrative international brain database. Markers are identified from the wide range of brain and cognition measures in the database enabling Personalized Medicine: linking the right brain health solution to the right person at the right time. Clients include half the top 10 global pharmaceutical companies and a wide range of clinical users in 9 countries.



Dan Segal
Chief Operating Officer
dans@brainresource.com

Summary

Sectoral transformation:

- Much progress has been made since our last update on the Personalized Medicine (PM) transformation of Healthcare in April 2004.
- There has been an on-going evolution of the enabling life science technologies underpinning PM, not least of which being standardized databasing and a myriad of new genomics tools which are leading to new Markers.
- In our view, PM is the next phase of the digital wave. Insights from the wave's previous impacts have relevance and buoy confidence in PM's prospects for delivering meaningful change.
- PM offers improved Healthcare, better risk management and cost efficiencies from being able to better match the right treatment solutions to the right person at the right time. These efficiencies are most timely given the predictions that US Healthcare spend may soon reach 20% of Gross Domestic Product.
- PM could meaningfully impact economic growth and be beneficial to the majority, including the pharmaceutical companies, with inefficiency the biggest loser.
- The move away from population based medicine to a more personalized and quantifiable approach represents a structural change. This requires the challenge of aligning the various constituencies (regulators, payer/reimbursement models, clinical practices with entrenched approaches) to embrace change. Thus far, what has been most encouraging is the leading role being taken by the US Food and Drug Administration and the Department of Health and Human Services.

BrainResource uniquely positioned:

- BrainResource is generating revenues from PM today. Brain testing services are being provided for both the WellBeing and Disability Markets. Users include pharmaceutical companies, clinicians, Managed Care (health care management and insurance providers) and academic researchers. BRC has delivered services to 12 global pharmaceutical companies and just under 30 research and development trials. BRC services are also being used in more than 150 clinical and other sites in 9 countries.
- BrainResource is differentiated by a standardized methodology and uniquely large integrative international brain database. The database now numbers over 20,000 datasets. Growth is aided by a feedback loop whereby growth powers new solutions which in turn drive customer growth which drives growth.
- BrainResource is developing a pipeline of solutions through a number of Marker discovery studies currently underway, the largest of which being the \$18m 'International Study to Identify Markers that allow the Prediction of Optimized Treatment Response' contract. An ability to deliver clinically useful and cost effective solutions represents a significant opportunity to add value, particularly given the large numbers afflicted by the brain health issues being addressed.

1. Personalized Medicine background

The Brain Resource Company Limited's (BrainResource) initial publication³ in April 2004 *Enabling Personalized Medicine* concluded that "a sectoral shift in healthcare (drug development and treatment) was underway. The current practice of 'population based' treatment is shifting towards 'personalized medicine' ". It also drew attention to the highly constructive proactive role being played by the US Food and Drug Administration's (FDA) initiatives, anchoring and catalyzing this shift. The FDA's 2004 seminal publication on the Personalized Medicine transformation was 'Innovation or Stagnation? Challenge and Opportunity on the Critical Path to New Medical Products' by Dr Janet Woodcock and her team at the FDA. This publication highlighted problems in the drug development pipeline and with flow on consequences to clinical treatment.

The FDA has continued to drive change, aided by a growing number of supporters⁴. Most recently, the US Department of Health and Human Services (HHS) issued 'Personalized Health Care: Opportunities, Pathways, Resources' (September 2007). The foreword by Michael O. Leavitt, Secretary of Health and Human Services included a succinct summary of PM and the state of the art:

"Personalized health...is health care that works better for each patient, based partly on scientific information that is new and partly on technology to make complex information useful. Personalized health care is about a transformed role for information in health care...Where once physicians had to practice medicine much like an art form using macroscopic tools to alleviate symptoms, personalized health care will provide molecular tools and information technology support to deliver care with greater precision, confidence, and individualization. Patients will have the opportunity to...take more responsibility for their own health care. Experiencing fewer side effects and better efficacy of treatment, patients will be more likely to engage in their personalized treatment and management plans...As such, they may be increasingly interested in assembling their own health care information, including individual genetic profiles, family history, past treatments, even personal preferences, into health portfolios – analogous to financial portfolios – to be managed with the help of health care planners, managers, and coaches."

Personalized Medicine (PM) rests upon Markers, which provide objective personal information on which Healthcare decisions can be based. Possibly the best known Marker is cholesterol (or to be technically correct, elevated levels of the low density lipoprotein), which can be quantified and used as an indicator of cardiovascular health. The timeliness of PM has arisen through an increased ability to identify a much wider range of relevant Markers across disorders through technological advances.

As an aside, we consider the more commonly used term, Biomarkers, to be a subset of Markers. Biomarkers are generally defined as characteristics that can be objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes or drug response (commonly used to refer to Genomics, Proteomics, Metabolomics). We also include characteristics that can be objectively measured from the brain: electrical function; blood flow; structure and cognition (social and general). The key issue being to include any stable Markers that allow identification of who will benefit from which treatment and who is at risk of non-response or adverse side effects.

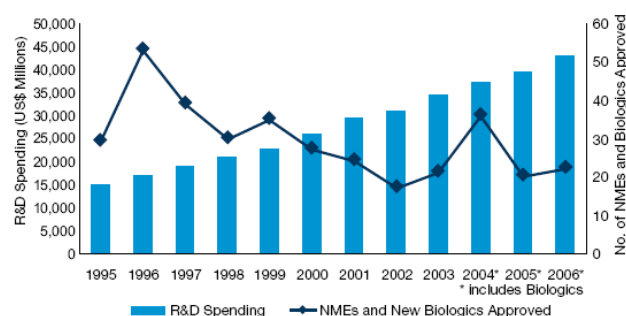
BrainResource – Personalized Medicine 2007 Update

1.1 Specific Healthcare challenges that PM can help address

The following are specific issues currently facing Healthcare. While we are not claiming that PM is the silver bullet cure all, it can make a significant contribution. PM is about delivering better information for treatment decisions, with Markers providing a quantitative basis for those decisions. As we will show, this translates into both treatment and cost efficiencies that are requisite to address the following problems:

- i. Health care spending in the US is estimated to reach above \$4 trillion by 2016 and comprise just under 20% of GDP⁵ (including the stimulus from the aging population). This growth is clearly not something that is affordable.
- ii. Declining Pharmaceutical company R&D productivity has led to depleted patent protected portfolios. The charts below taken from a PriceWaterhouseCoopers report⁶ shows that (right chart) R&D spending continues to grow disproportionately to new drug approval and (left chart) new drugs are not being developed at sufficient a pace to replace existing drugs coming off patent. For example Pfizer has 41% of revenues exposed in the next few years. It has been reported that for the year to October 2007, only 15 drugs (new molecular entities or NMEs) have been approved.⁷

Company	2010	2011	2012	Share of Revenues (%)
AstraZeneca	Arimidex (\$2.2bn)*	Seroquel (\$4.7bn)	Symbicort (\$3.7bn)	38**
BMS		US Plavix Avapro (\$1.3bn)	Abilify (\$2.1bn)	30
GSK	Advair (\$3.8bn)		Avandia (\$2.5bn)	23
Eli Lilly		Zyprexa (\$4.8bn)		22
Merck	Cozaar/ Hyzaar (\$3.2bn)		Singulair (\$4.5bn)	22
Novartis	Femara (\$1.1bn)		Diovan (\$6.0bn)	14
Pfizer	Aricept (\$800m)	Lipitor Xalatan (\$1.6bn)	Viagra (\$1.7bn) Detrol (\$860m) Geodon (\$1.1bn)	41
sanoofi-aventis	Taxotere (\$2bn)	US Plavix Avapro (\$2.1bn)	Lovenox (\$3.1bn)	34

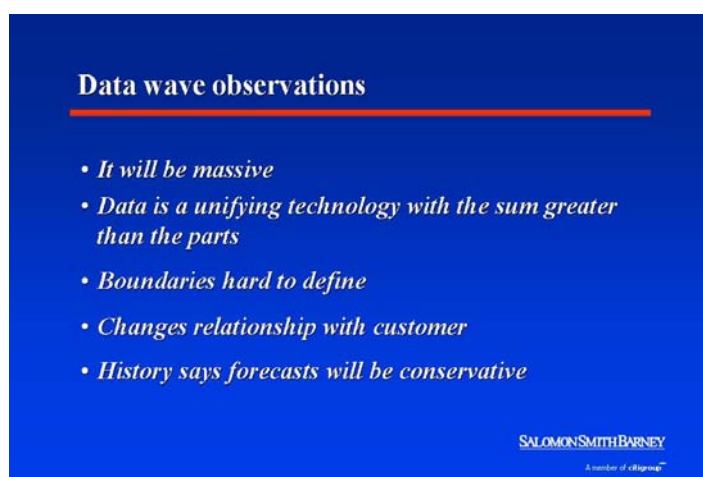


- iii. The UK's National Institute for Health and Clinical Excellence (NICE) agreed to buy a cancer treatment made by Johnson & Johnson that has little effect on a third of patients, on the condition that it would only pay when the drug works. *“For those who may get a full response or a partial response...it’s a cost-effective intervention for the National Health Service...Narrowing down to patients getting the best response makes it worth it.”* Andrew Dillon, NICE Chief Executive⁸. The current model for pharmaceutical sales is they get paid irrespective of whether or not the treatment works.
- iv. Adverse events continue to plague Healthcare. A recent US study has shown that from 1998 through 2005, reported serious adverse drug events close to tripled to just under 90,000pa⁹. The increase was influenced by relatively few drugs, with 298 of the 1,489 drugs identified (20%) accounting for 87% of the events. The study could attribute a quarter of this growth to increased prescriptions and 15% to the introduction of new biotechnology drugs since 1998, but the rest could not be explained. Five of the top six drugs causing deaths were painkillers, with the sixth an antipsychotic (Clozapine). The most common drugs causing nonfatal adverse events were: Estrogens, Insulin, Interferon beta (MS/Cancer), Paroxetine (Depression), Clozapine (Schizophrenia), Oxycontin, Warfarin (anti clotting agent) and Fentanyl.

2. The digital wave now driving Healthcare

PM is the culmination and convergence of the many advances in the life sciences over previous decades which, through computing power, are now able to be harnessed into new tools. This is best exemplified in Genetics where the power of the initial DNA and related discoveries are now being unleashed in mass market products, underpinned by computer processing power to collect and process the massive datasets required to extract meaningful information. Other enablers of PM are discussed in Section 3.

Given these technology drivers, PM is showing many of the hallmarks of the previous industry transformations arising from the digital revolution, with its same share of enthusiasts and skeptics. The following slide was taken from a November 1998 presentation of mine¹⁰ about the transformations then underway in the telecommunications sector. As illustrative of the comparability, my view is that these same conclusions could apply equally to PM (that is substituting the word Data with PM).



My optimism about PM's prospects, while based on its ability to deliver solutions to the abovementioned problems, also factors observations of the power, breadth and speed of these previous transformations on which PM is building. Accordingly, before dealing with these specific PM drivers (see Section 3 following), my view is that there is important insights to be drawn from looking at the broader digital wave and its impacts to date, what worked and why, when assessing PM prospects.

There are also many similarities between current PM attitudes and the following: *"The growth potential of the Internet lends itself to both pessimistic and optimistic expectations. The pessimist, having struggled through descriptions of legal uncertainties, competitive concerns, and bandwidth bottlenecks, will be convinced that all these problems can only become worse as the Internet grows. The optimist, on the other hand, recognizes that technology and markets have proven their ability to solve problems even faster than they create them."* Federal Communications Commission: Digital Tornado: The Internet and Telecommunications Policy (March 1997).

There are of course many distinguishing features between transformations, but two stand out. PM addresses the above problems, which are enormous and in need of urgent solutions. By contrast, no government in the 1970's was focused on solving the

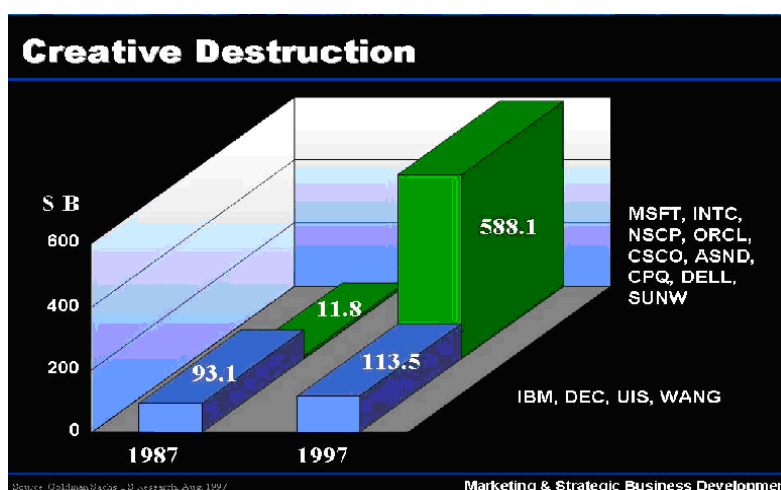
BrainResource – Personalized Medicine 2007 Update

problem of how to empower an average person to search for information more efficiently. Everyone is impacted by Healthcare and the ambit for productivity gains is better treatment, lower costs and possibly most important, improved risk management through a greater ability to predict disease states and treatment outcomes.

2.1 Previous transformations of the digital wave

The first impact of the digital wave was the automation of business administration which transformed manual systems, including payroll, customer order processing, inventory management, etc. The catalyst for change was the invention of the mainframe computer, with the inflection point arising from computer processing power becoming more readily available to big businesses in the 1960s. IBM was a major player in this market.

This transformation then fed the next phase and impacted with greater power and consequences than the first. The computer industry was itself transformed by the PC in the first instance and the networked PC in the second. This saw many rapid shifts in value, shown below, with the dominant value accreting to new entrants¹¹.



The wave then moved to transforming communications and a wide range of retail commerce and entertainment (including telecommunications, internet, mobile telephony, entertainment, auctions, shopping, banking, etc) in the 1990s. The types of change were broad, ranging from internal production efficiencies to new product opportunities to product replacement. The internet provided a distribution network with unprecedented reach and access to all.

The critical driver for uptake was the ability to personalize the experience. No longer did you have to accept only what was for sale at the local mall nor read only the local newspaper. This was described by George Gilder¹² *“The critics of the Internet are mostly skeptical about the value of choice. But choice validates freedom and substantiates individuality. Choice accords with the inexorable genetic diversity of humans.”*

The commercial attractions are best described by Anderson’s theory of the Long Tail¹³ which is that our culture and economy is increasingly shifting away from a focus on a relatively small number of "hits" (mainstream products and markets) at the head of the demand curve toward a huge number of niches in the tail, where many products are in low demand. They key being that the tail can collectively make up a market share that

rivals or exceeds the relatively few current bestsellers and blockbusters. An example cited is iTunes where almost every one of their 6m or so tracks in inventory sells at least once per quarter.

2.2 A snapshot of winners and losers from the above transformations.

Transformations are complex, with many factors influencing outcomes. Accordingly, the following are some of our generalized observations¹⁴ of factors that appeared influential. These may have relevance for strategic consideration as part of the PM transformation.

- Technology transformations follow the usual rules of economics but the scale of impact forces management to examine and re-examine each business assumption, to avoid jumping at shadows as the running of the bulls accelerates.
- The internet boom did not change the need for a business to have content, distribution and a way of getting paid.
- Companies needed both distribution and content, with at least one needing to be unique (eg Google has unique content and common internet distribution, telecom companies have unique distribution networks).
- Content needs to be monetizable (Google benefits from the unique synergy between search content and advertising revenue) and growth in customer numbers alone did not assure profits (eg many telecommunication / internet companies).
- The digital wave can radically change old established rules. One example is the music industry, while having content, experienced a diminishing ability to get paid as copyright law became hard to enforce as the distribution floodgates opened.
- Incumbents faced a daunting challenge to both see change coming as well as making the requisite radical decisions to adapt. Bill Gates was one who did just that in changing the entire Microsoft focus to adapt to the internet. Most were slow to respond (eg many telecommunications companies remained carriage providers as opposed to benefiting from the value of what was carried).
- Incumbents with unique content and capable management, even where they moved slowly, saw through change (News Corporation) although some ended up with different business models to when they started (IBM).
- Half-hearted new initiatives generally resulted in write-offs. Mergers and Acquisitions and cost cutting in the main provided at best only band-aid solutions. These initiatives, in the main, eroded shareholder value (Worldcom/MCI, ATT/TCI, Time Warner/AOL, Telstra/PCCW).
- The best defense was innovation, with cost cutting and M&A its nemesis.

This was summed up by Warren Buffet on internet valuations just before the February 2000 collapse (in Fortune Nov 22, 1999): *“The key to investing is not assessing how much an industry is going to affect society, or how much it will grow, but rather determining the competitive advantage of any given company and above all the durability of that advantage. The products or services that have wide sustainable moats around them are the ones which deliver rewards to investors.”*

2.3 The digital wave is now at the start of transforming Healthcare

The following table summarizes the rolling nature of this wave and also the progressive buildup of power as each sector is transformed. That is, communications relied on the changes that preceded in business administration and retail relied on changes from both

BrainResource – Personalized Medicine 2007 Update

of the previous transformations. Similarly, Healthcare builds upon changes in all three previous transformations.

	Transformed Sector			
	Business Administration	Communication	Retail/ Entertainment	Health/WellBeing
Catalyst	Semiconductors	Computers	Relational Databases	Relational Databases & new life science technologies
Inflection point	PC Specification	Internet Protocol	WWW & Data mining software	Predictive Markers
Key paradigm	Moore's Law ¹⁵	Metcalfe's Law ¹⁶	Anderson's Long Tail	Personalized Medicine
Key player/monetization	Microsoft/ software	Cisco/ hardware	Google/ advertizing	Incl. BrainResource /health services
Key strategy concept	Embrace & Extend	Acquisition & Development	Contextual adverts / Anything, anytime	Match Markers to solutions
Key obstacles	Technology limitations	Regulatory Framework	Payment systems, Digital rights	Privacy protection, entrenched model, alignment of many constituencies
Key Benefit	Dramatic productivity improvement	Dramatic productivity improvement	Dramatic productivity improvement	Dramatic productivity improvement & Risk Management
Key player market value	\$350bn	\$200bn	\$220bn	Early stage

2.4 Personalized Medicine will evolve

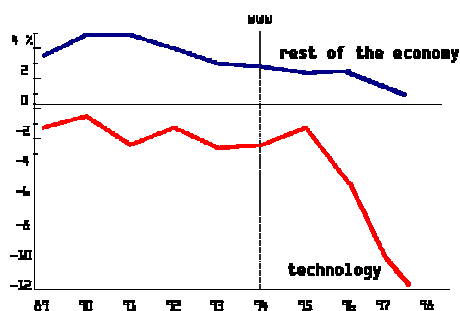
PM will over time mean many things. By way of example, some have started to build an expectation that PM includes developing a specific drug/treatment to cater for an individuals unique characteristics as opposed to identifying what drug/treatment from those commonly available is best suited to an individuals characteristics. While the former is appealing and may eventuate, it is practically beyond our current reach. The focus is therefore currently only on the latter. We share the view of the US Secretary of Health (<http://secretarysblog.hhs.gov/>):

"I worry when we use the phrase personalized medicine, for some, it creates a mental picture of a patient having one-of-a-kind pharmacology developed specifically for them, based on their phenotype, environment and genetic make-up. The vision we are moving toward, in my mind, is best described as mass personalization. Using a thorough understanding of a person's genetic and clinical history, a doctor will select a combination from a group of biological and chemical treatment tools....We have the technology now to make health care much more personal and much more efficient."

2.5 Strong economic contribution

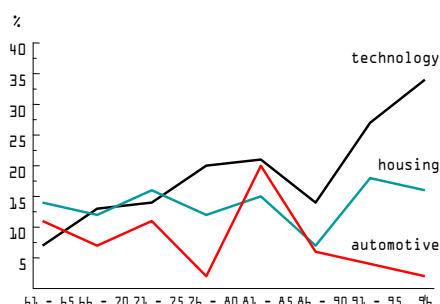
In light of the above need for increased Healthcare efficiencies, it is worth noting the economic benefits of the previous technology wave¹⁷. While I am not claiming that Healthcare would enjoy the same degree of gains, there are still significant gains to be had from the efficiencies PM introduces, including direct cost savings and also productivity gains from improved treatment.

inflation by sector



Source: Bureau of Economic Analysis, BEA 9997/98

contribution to economic growth



source: bureau of economic analysis, usa 1997

3. Catalysts and Enablers of PM

3.1 FDA driving role together with the US Secretary of Health.

Given the high degree of regulation of Healthcare, progress would be difficult without regulatory support. The FDA continues to play a leading role in PM, in many ways driving the thought process ahead of many corporates. This is demonstrated by the following on-going FDA initiatives:

- Guidance on Pharmacogenomics data - issued November 3, 2003.
- Innovation or Stagnation? Challenge and Opportunity on the Critical Path to New Medical Products - issued March 16, 2004
- Critical Path Opportunities Report & Opportunities List – March 2006
- Critical Path Opportunities Initiated During 2006 – Press release February 2007
- Pharmacogenomic Data Submissions — Companion Guidance – August 2007
- FDA Clears Genetic Lab Test for Warfarin Sensitivity – September 2007

There have also been recent reports from the Department of Health and Human Services which add to this progress, including the report referred to above and a November 2007 Draft Report from the Secretary's Advisory Committee on Genetics Health and Society dealing with the oversight issues relating to genetics testing and its role in delivering PM¹⁸.

3.2 Standardized Databases integrating new technologies

Our view is that standardized Databases are among the most important enabling factors, in that they anchor and empower a wide range of both the existing and new technologies. Databases allow converging evidence to be identified and new insights to be extracted, providing the evidence base for any new emergent PM solutions. Healthcare Databases are evolving through many phases:

- Phase 1: disease and treatment generic information – this phase is now quite mature in terms of there being websites to cater for virtually every health information need.
- Phase 2: personal data repositories (or electronic records) – this phase is still to commence with many governments tied up in all the problems that these repositories create, most notably privacy. It is interesting to note that sites like MySpace have not been bogged by these issues. In recent developments, Microsoft, Google and RevolutionHealth (founded by AOL founder Steve Case)

- to name a few have either launched or are launching these repositories which will allow personal data to be stored and selectively accessed.
- Phase 3: active personal data repositories including: (1) more complex medical data such as that acquired using newer technologies; and (2) with the power of both being able to be mined to identify new personalized Markers and able to evaluate personal response factors, including to drugs, leading to improved treatment.

Possible causes for the slow introduction of Health Electronic records by Governments could be tied to the challenges presented by databasing that were well described in a Nature¹⁹ review article. This pointed to the barriers being: reaching a consensus on what to include; technical challenges of how to include, share, analyze and use data; and overcoming the propensities to not want to share hard won data.

Monetizing the first two phases may prove more complex than the third. Thus far, analogous sites have monetized value from the nexus between search and advertizing. This link is not obvious in these cases but instead of an advertizing source there is the real opportunity to monetizable the range of consequential increased Healthcare efficiencies. Phase 3 is possibly the most interesting as this begins to harness the power to mine data for new insights and also to benefit from the power of feedback loops. Again using the telecommunications precedent²⁰, databases can be substituted in place of the internet in the following:

“...it is valuable to understand the Internet as a feedback loop. A feedback loop occurs when the output of a system is directed back into the system as an input. Because the system constantly produces fuel for its own further expansion, a feedback loop can generate explosive growth. As the system expands, it produces more of the conditions that allow it to expand further. All networks are feedback loops, because they increase in value as more people are connected. The Internet, however, is driven by a particularly powerful set of self-reinforcing conditions.”

As an aside, the Brain Resource International Database is an exemplar of Phase 3. The abovementioned challenges have been overcome and the database is now harnessing the power of feedback whereby growth in the database powers new solutions which in turn drive customer growth which drives growth in the database.

3.3 Example of new data acquisition technologies - SNP chips

There are many new technologies beginning to enter the field that allow for personalized data to be cost effectively acquired. Most notable among these are the SNP Chips which allow large scale identification of DNA sequence variations to be identified through looking at the Single Nucleotide Polymorphisms (SNPs)²¹. These variations can inform on an individual's predisposition to disease or how they respond to a drug.

Currently, a single matchbox size chip can look at 1 million variations. This technology has seen rapid development, with the growth in power of these chips over the last 18 months surpassing Moore's Law (for semiconductor chips) in being up almost 10 times. Prices by our estimates, assuming constant power of the chip, have more than halved in less than 12 months. Extracting and analyzing this amount for even one subject rests on computer power and databasing.



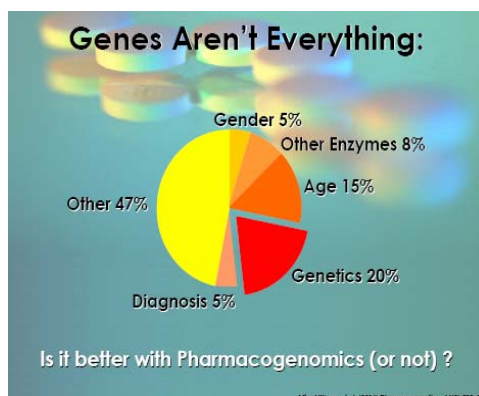
There are a myriad of other new technologies including those covering

Genomics, Metabolomics, Proteomics. BrainResource brings together many Genomic-Brain-Cognition measures that are usually assessed in isolation to identify Markers (see later discussion on the BrainResource database).

3.4 PM not only about genetics

In many ways, the face of PM thus far has been genetics. Genetics has also been the focus of intensive R&D by drug companies. Genetics are important. However, the heavy reliance on only using genetics to characterize individual traits, in our view, has significant shortcomings. Genetics primarily only provides information on hereditary disease risk and treatment predisposition. It provides a limited view of disease progression and any impacts from either environmental factors or other self inflicted considerations, for example stress, diet, trauma, etc. Moreover 80% of the 25,000 human genes have some effect in the brain, arguably resulting in many genes underpinning each brain disorder.

This point has been well highlighted in a publication looking at the factors influencing the dosing of the blood thinning drug Warfarin²². The following slide shows that genes are not everything.



A recently completed large scale genetics study²³ found “for any given trait there will be few (if any) large effects, a handful of modest effects, and a substantial number of genes generating small or very small increases in disease risk.” This led to the following descriptive observation:

“If that is the case, the existing paradigm of drug discovery and development requires radical rethinking, as does the concept of personalized medicine based solely on genetics. Exit the silver bullet and enter the carronade (the carronade was a short-barrel, large-diameter cannon that could be loaded with a canister of 500 musket balls)”²⁴.

Further, as has been seen in many studies to date, assessing genetics in isolation can be unproductive given that the large numbers of candidate genes that can be identified, and weeding out which ones really matter a daunting challenge.

BRC was founded on our view that only a ‘carronade’ approach will deliver outcomes in studying the brain given the high degree of interplay between genetics and environmental factors. Further, unlike most other organs, the brain is not one-dimensional e.g. the heart has one function: to pump blood. Accordingly, BrainResource has for example shown there to be much power that is gained from converging insights from different technologies²⁵. This includes helping to identify which of the on-going stream of candidate genes being discovered are worth targeting for drug development.

4. Business case considerations

PM covers a broad spectrum. The economics can therefore not be considered as if it is one product. PM and the consequential improvements in information have more value in some situations and less in others, impacting users differently. What is unambiguous is that better information is now available and profitable when selectively used.

My view is that all groups at some level benefit from PM:

- Patients: currently suffer from delays in finding the right treatment which also leads to poor compliance (do not persist with treatment).
- Clinicians: time pressures and inefficiencies in treatment process.
- Government payers: massive cost to society and direct costs of funding.
- Private payers/Managed Care: have to manage rising costs and maximize efficiencies.
- Pharmaceutical companies sales & trials: high failure rates, growing costs, sales impact from poor compliance.

The success or failure of Personalized Medicine in our view rests with the regulators, those paying for healthcare and also the pharmaceutical companies. The technology continues to show value. However, like any industry, without distribution great technologies can stagnate. Healthcare is also highly controlled and regulated so without support, reaching the tipping point will be that much harder. The following sets out my views as to the benefits for the two major groups. I have not dealt with specific individual benefits as my assumption is that PM leads to improved care. As with anything, there is always room for exploitation but there are enough checks and balances in the system to minimise this risk.

As an aside, most Healthcare systems can not meet demand. Thus increasing efficiencies through PM and alleviating pressures should also not have a direct negative impact on service provider returns. To illustrate this point, a recent report about medical tourism suggests that if every US resident who could go abroad for treatment actually went, the savings on total medical costs would be about 5%, or less than half the existing growth rate²⁶. Those most exposed from PM are those selling inefficient solutions, for example, those selling a drug which does not work in the majority of users (losers will also include those risking development of new solutions, including Marker discovery, that fail).

4.1 Managed care/Government payer groups

PM's introduction is compelling where there is an increased patient benefit at no additional cost or a cost reduction with no deterioration in patient care. That includes whether the cost of a PM test is priced at a level below the current process that it replaces, for example below the cost of a saved clinical visit or additional drug prescription. There is also the additional practical issues of whether the PM test is something easy to administer and roll out.

The decision is far more complex where patient benefit and cost both rise from PM. This then requires the less objective decision to be made as to whether the improved patient benefit is cost justified within overall budgetary constraints.

There will of course be many situations where one solution has widespread benefit and others where PM does not add sufficient benefit to the patient care nor contribute to any cost savings. For example, it would be very tough to justify any PM testing for a drug like Aspirin.

(a) Warfarin example - \$1bn PM cost savings

Around 2m patients start taking Warfarin (a blood thinning drug) in the US per year. Warfarin is the second most common drug, after insulin, driving emergency room visits for adverse drug events, causing an average of more than 43,000 cases per year in 2004-2005. The challenge is therefore to find the optimal dose, which varies greatly from person to person. If the dose is too high, users are subject to increased risk of serious bleeding and if too low, subject to increased risk of stroke.

The FDA recently updated the drug label to explain that people's genetic makeup may influence how they respond, with the opportunity for Healthcare providers to use genetic tests to improve their initial estimate of what is a reasonable Warfarin dose for individual patients.

The health care savings from PM using genetic testing (for the two genes CYP2C9 and VKORC1) in the Warfarin therapy have been estimated²⁷ to reduce health care spending by \$1.1 billion annually (\$1.15 billion in reduced bleeding costs + \$675 million in reduced stroke costs - \$700 million testing costs). These assumptions did not however factor any indirect savings arising from the value of the health improvements among Warfarin users. They also did not factor volume discounts in the cost per genetics test²⁸.

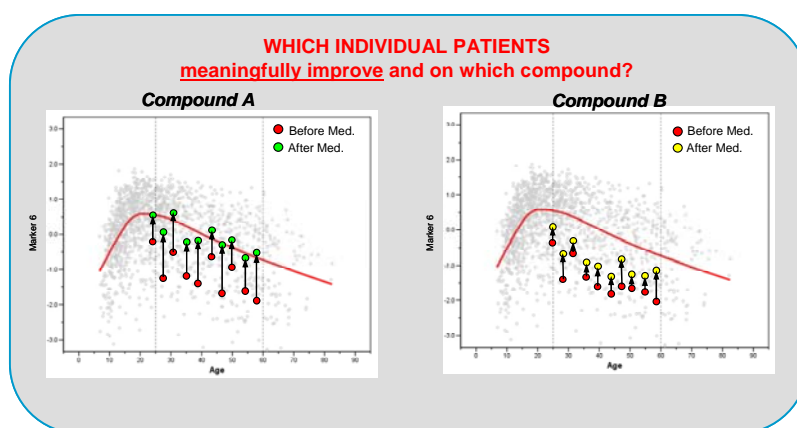
4.2 Pharmaceutical companies

We consider the impact on Pharmaceutical company Research & Development (R&D) and Sales divisions separately.

(a) Research and Development

As discussed above, there is a paucity of new drugs to replenish those coming off patent. It takes about 10-15 years to develop one new medicine from the time it is discovered to when it is available for treating patients. The average cost to research and develop each successful drug is commonly estimated to be \$800 million to \$1 billion. This number includes the cost of the many failures: For every 5,000 to 10,000 compounds that enter the R&D pipeline, ultimately only one receives marketing approval.

Markers offer R&D efficiencies though being able to: (a) better select patient groups; (b) deliver more quantifiable end points against which progress of a trial can be assessed; and (c) determine relative performance between candidate drugs in inventory. The graphs below show the power of having a database Marker baseline against which relative performance can be measured. There is also the very substantial issue of understanding placebo responders.



Having reliable trial screening end points (Markers) can reduce cost. Like solving any problem, better quality information lets you see which paths are working quicker as well as those that are not. Given the high costs, failing a non performing drug candidate fast can deliver significant savings. As an aside, there is also the need to ensure that progress is aligned with the abovementioned FDA stance.

- i. Herceptin example - \$2.5bn PM revenue acceleration

The ‘poster child’ of PM is the antibody drug Herceptin (trastuzumab), which effectively treats breast cancer in women who have uniquely presented with over-expression of a cell surface protein, known as Human Epidermal Growth Factor receptor 2 (HER2)²⁹. Having this marker allowed for a smaller faster trial to be undertaken. Most significantly, as the lifetime for patent protection is finite, the faster path to market meant a longer patent protected sales cycle worth billions³⁰.

Example Herceptin: The Business Case for Subdividing the Target Population

Trial Design	With HER2 neu	Without
# of patients	470	2200
Response rate	50%	10%
Years of follow-up	1.6	10

- Savings in clinical trial costs ~ \$35 million
- Income from 8 year acceleration of product ~ \$2.5 billion
- Access to drug from acceleration ~ 120,000 patients
- Recent success in adjuvant therapy ~ Value extension

* From Press and Seelig, Targeted Medicine 2004, New York, November 2004

Of course, there are also benefits of having the HER2 test in the market. The relative cost (around \$400 per test) is small when considered against the benefits – that is the faster treatment of patients that will respond and not wasting precious time on the wrong treatment path for non-responders and cost. It is also small relative to the cost of treatment which can run into many tens of thousands of dollars per annum.

BrainResource – Personalized Medicine 2007 Update

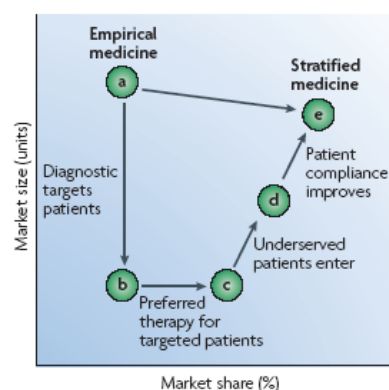
(b) Sales

Included in the PM skeptic armory is that Pharmaceutical companies have much to lose from PM in terms of losses in revenues from a more targeted use of medications. My view is that this risk is overstated and is relatively small compared to other risks to sales from say changes in regulation or litigation from failed medications. To the contrary, my view is that PM could enhance sales, on average.

At the outset it is worth pointing out that many drugs are not exposed to this risk. For example Herceptin increased returns, from sales of a drug that without PM may not have ever been approved, and Warfarin reduces indirect costs but not necessarily drug sales. However there will be circumstances where losses in sales do occur. The issue is then whether these lost revenues, from patients who no longer take the drug due to no predicted benefit, can be recouped elsewhere.

The underlying assumption is that the drugs do work, albeit in select people. There are several sources for Drug A to recoup losses (also shown pictorially³¹ on the right with stratified medicine referring to PM):

- capturing spillage from other drugs with no predicted patient benefit where Drug A would benefit;
- new patients entering from increased probability of finding a solution – patients greatest concern is will this drug hurt me, with an increasing confidence translating into new customers considering treatment where before PM they would not.
- positive impact from increased compliance by those benefiting – the faster a patient can find a solution, the more wedded they will be to using this solution for a longer time.



A simplistic calculation highlights the potential that this potential risk of sales erosion could actually be smaller than many think and could actually deliver better returns, on average.

The loss in sales from PM is tied to the percentage of responders to a drug. Where this is between 20-60%, we estimate that the amount of sales that could be lost (or to be recouped) to be somewhere between 5-20% of sales. The key assumption is that those that benefit from a drug take it for 12 months, with those showing no benefit cease after 1 month. Clearly, if a non responder takes a drug for an extended period, say equal to the period of a responder, then the loss in sales will be greater. Hence there are situations where PM losses could be substantial with the ability to recoup marginal. This calculation also assumes no significant customer acquisition costs, which would offset the loss in sales. This is not impossible given the massive budgets for drug advertising and marketing.

5. BrainResource Personalized Medicine solutions

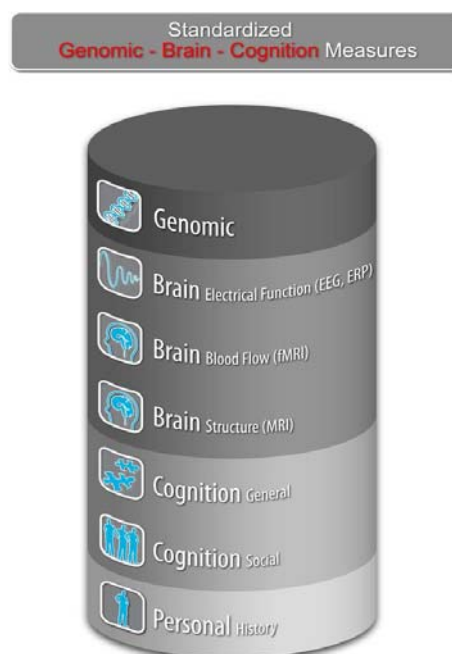
BrainResource is focused on brain Marker discovery using its unique standardized methodology and large scale integrative international brain database. The wide range of brain and cognition measures are used to identify Markers that enable the right brain health solution to be reliably linked to the right person at the right time. This has application to both WellBeing (that is to pre-empt the need for clinical visits or drug therapy or merely to improve performance) and Disability (helping clinicians to predict the most optimized treatment).

BrainResource has an ongoing program of Marker discovery (both internally and externally funded) covering a range of disorders including Alzheimer's dementia, Depression, Schizophrenia, Bipolar Disorder, Attention Deficit Hyperactivity Disorder and Anxiety Disorders.

5.1 Standardized methodology

BrainResource is differentiated by a standardized methodology and uniquely large integrative brain database. This database brings together a wide range of technologies (see right) to help make sense of human brain function and cognition and with the requisite scale.

BrainResource's standardized process allows users anywhere in the world to collect brain data in exactly the same way using a range of web, touchscreen and laboratory based data acquisition platforms. This data is then sent to BrainResource for analysis including against the database.



5.2 BrainResource Marker development well aligned.

BrainResource's Marker development and approach is explicitly aligned with the direction being heralded by the US Food & Drug Administration (Critical Path Initiative) and American Psychiatric Association (Diagnostic and Statistical Manual of Mental Disorders – DSM V).

“Today, diagnosis of psychiatric disorders is based on symptom presentation. There are no diagnostic tests to distinguish an initial presentation of depression from the onset of bipolar disorder or other conditions. Identification of such Biomarkers would improve clinical trials by making it possible for sponsors to enroll only those patients with the target condition. Similarly, any successful treatments could better target a patient's disease in clinical practice.” Source: Food & Drug Administration April 2006.

BrainResource – Personalized Medicine 2007 Update

BrainResource approach is in line also with that of US Department of Health and Human Services in that *“We can recognize the importance of collaboration.. the need for standards... imperative for collaboration across the private and public sectors...across many disciplines. Making use of genomic profiling tests, large databases of predisposing factors, sophisticated monitoring devices that provide data in real time, and streamlined electronic patient records, physicians will better prevent disease, predict outcomes, and help patients heal faster through personalized care.”*³²

5.3 Wellbeing

Wellbeing is about Prevention, which is better and less costly than needing a cure. Early identification of problems increases the chance of there being interventionist measures that could help keep a person away from requiring a clinical intervention. This included in the workplace where there is currently an escalation in demand for valid and reliable behavioral management tools to augment existing Health Risk Assessments

BrainResource’s Behavioral Management System has emerged from our scientific resources and database approach. It is a suite of products which allow large groups of individuals to be managed using quantifiable evidence-based Markers. It is focused on the screening, streaming and monitoring of individuals enabling cost effective service delivery, assisting the identification of personalized solutions

The three levels of assessment are:

- baseline screening of a large population for social cognition (anxiety and mood);
- for those flagged with problems with social cognition, an assessment is then conducted into their general cognition (e.g. memory, attention, emotion recognition, speed) which establishes the level and extent of the disability allowing appropriate streaming into treatment groups; and
- regular monitoring of both social and general cognition capacity after they begin treatment to measure response to treatment. Those not flagged in the initial broad screening are reevaluated every 12 months, the others every three to six months.



5.4 Disability and new drug Research & Development

The largest of the BrainResource Marker discovery studies underway is the \$18m “International Study to Identify Markers that allow the Prediction of Optimized Treatment Response” (‘iSPOT’), focused on Depression and Attention Deficit Hyperactivity Disorder (ADHD).

iSPOT is about increasing the bar for diagnosis and classification of psychiatric diseases – moving the current reliance on the observation of signs and symptoms (with its high degree of subjectivity) to a more quantitative basis. This also applies to the selection (or non selection) of medications by the clinician which is also subjective.

For example, there are currently no reliable Markers or valid behavioral tests which define the precise nature of Depression or ADHD, and a recent review of the psychometric properties of a commonly used scale (HAMD) that rates patient responses for Depression, concluded that the test was both psychometrically and conceptually flawed. Given the numbers suffering from these disorders, there is a need for valid novel objective Markers, tied to the underlying biology, which are sensitive to an individual’s particular needs and that can reliably predict treatment response or non-response for a particular individual. Further, while a range of candidate gene associations have been made, they have not always been tied back to a range of other brain and cognition measures making it difficult to distinguish respective values.

Delivery of meaningful outcomes requires iSPOT data to be collected (a) from large subject numbers pre and post medication and (b) using a wide variety of data acquisition technologies for each subject. The aim is to identify both evidence-based diagnostic and treatment predictive Markers (using four drugs selected from those currently on the market). iSPOT is to be conducted internationally at around 30 sites including in the US, UK, Australia and others and will acquire integrative data from 4,000 subjects. BrainResource’s standardized and integrated approach and breadth of technologies has the capabilities to deliver the requisite unprecedented scale of this study.

Successful identification of these Markers would have widespread benefit. Markers could better enable clinicians to target a patient’s disease and help to match the right drug to that person, thereby delivering significant cost and treatment efficiencies. The efficiencies of clinical drug trials could also be enhanced, by making it possible for sponsors to enroll only those patients with the target condition and to better assess progress. Further, the data may also point to new drug candidates for future drug development.

To give context to the scale of iSPOT, the most recent major study was funded by the US Government. STAR*D (‘The Sequenced Treatment Alternatives to Relieve Depression’) was a \$35m study over 6 years and enrolled 4,000 outpatients from 41 clinical sites across the US. This study was had a slightly different focus in that its concern was on the common clinical questions of what to do next when patients fail to respond to a standard trial of treatment with an antidepressant medication. Most importantly, the study used rating tools of symptoms and side effects to identify response. This compares to BrainResource’s full standardized integrative measures.

iSPOT is being funded by a private biotechnology company and under the terms of the agreement BrainResource also benefits from successful outcomes, through the retention

of a significant interest (by way of license) in the intellectual property created or contributed by BRC under this agreement.

5.5 Monetizing Brain Behaviour Markers example

Our view is that for PM Markers to be commercially relevant, they need to provide solutions, that is, they need to point the way to a specific therapy. A diagnostic Marker only has clinical utility where it informs a solution. For example, diagnosis that does not point to a treatment is only clinically useful in limited situations (for example in workers compensation claims). We also concur with the view that the degree to which a Marker can be monetized is proportional to it being *“easy to use, robust and offer high throughput... potential winners will keep it simple”³³*.

Speculating over the iSPOT outcomes provides some insight into the challenges in commercializing Brain Markers. There are three issues that need to be considered in assessing the monetization prospects for iSPOT outcomes – or for that matter the other Marker studies underway:

(a) will iSPOT yield validated markers using BrainResource’s standard range of tests?

BrainResource has a large database and this together with specific precursor work provides us with a reasonable degree of confidence (that is as confident as one can be when doing groundbreaking novel science) that we are on the right path. Our view is that the Markers will be complex combinations using a range of our more than 100 standard measures, with the power of the Marker tied to the number of measures it includes. Our measures have different acquisition costs – ranging from minimal (for data collected over the web) to thousands of dollars (functional MRI).

(b) will an emergent competitor deliver validated markers before BrainResource?

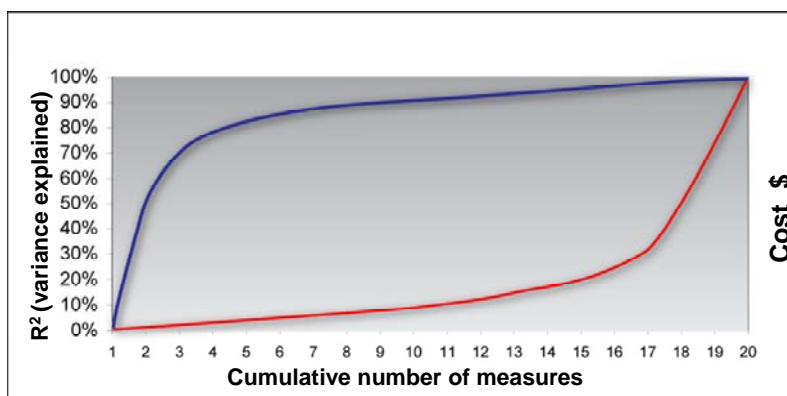
In terms of the competitive position, our standardized integrative database approach ensures that we cover a wide breadth of technologies and with large subject numbers. This is premised on the complexity of the brain. As far as we are aware, our database is unique in terms of standardization, breadth and scale. It is also not something that can be instantly replicated, technology issues aside, as merely collecting this amount of data is not trivial. Accordingly, the significant risk that BrainResource faces is that the sophistication of our approach is overkill and someone comes along and finds a tremendously powerful Marker from a simple test.

(c) will these markers be commercializable, that is, easy and cost effective to deliver?

This is possibly the harder call. The key point being that the Markers have to be easy to administer and cost effective, as opposed to merely being valid. What BrainResource will uniquely be able to deliver, given the breadth of measures, is a range of composite Markers with different powers (that is R^2 - the degree to which the marker can explain the variance and predict outcomes) and different price points, allowing users to make informed optimization decisions. Thus we may be able to offer a cheap low power Marker (but informed by the full breadth of tests) for widespread screening, or more costly Markers for those that have already been screened. Clearly, the cheaper the Marker, the greater the commercial appeal and the easier to administer, the more likely it will be used.

BrainResource – Personalized Medicine 2007 Update

The following graph shows the range of possible outcomes within a particular envelope. There are three variables to consider for each Marker: the power, number of measures needed to identify the Marker and the total cost. Ideally, Markers will be found with a cost profile of the bottom curve and a power profile of the top curve.



5.6 Hypothetical for commerciality of iSPOT

iSPOT is focused on identifying validated Markers for Depression and ADHD that would assist the diagnosis and treatment. If iSPOT is able to deliver Markers which expedite matching the right treatment to the right individual and if that marker can be sold at a price of less than the cost saving (clinical visits, lost productivity, etc) resulting in widespread use, this would represent a very significant market opportunity³⁴.

We can only speculate as to worth of such a marker, with extrapolations about new markets in as difficult field as the brain fraught with risk³⁵.

Leading Therapy Classes by Global Pharmaceutical Sales, 2006			
	Sales US\$bn	% Sales	% Growth
Lipid Regulators	\$35.2	5.8	7.5
Oncologics	34.6	5.7	20.5
Respiratory Agents	24.6	4.0	10.4
Acid Pump Inhibitors	24.1	4.0	3.9
Antidiabetics	21.2	3.5	13.1
Antidepressants	20.6	3.4	3.3
Antipsychotics	18.2	3.0	10.9
Angiotensin-II Antagonists	16.5	2.7	15.2
Erythropoietin Products	13.9	2.3	11.8
Anti-epileptics	13.1	2.1	10.8
Total Leading Therapy Classes	\$184.30	32.9%	10.7%

Source: IMS MIDAS®, MAT Dec 2006

The US accounts for around \$13bn of the above \$21bn global antidepressant sales value. Antidepressants are also the most prescribed drug in that market, with its 21m sufferers driving more than 230m scripts per annum³⁶. Making the simplistic assumptions that an Marker can be found that provides utility to 10% of those afflicted, at a bi-annual cost of say \$100 per test (compared to drug sales growth of around 3% p.a.), implies an annual gross sales value for the US market alone of around \$400m pa. This represents just over 3% of US antidepressant sales and an even smaller fraction of the overall more than \$30bn³⁷ of other economic costs linked with depression (including absenteeism, lost productivity, treatment and rehabilitation).

BrainResource – Personalized Medicine 2007 Update

- ¹ Extracted from a speech at the annual meeting of the Personalized Medicine Coalition, at the National Press Club, Washington (23 March 2007).
- ² E Gordon: Integrating Genomics and Neuromarkers for the era of brain-related personalized medicine. *Personalized Medicine* 4(2) 201-215 (2007), <http://www.brainresource.com/uploads/17410541.4.2.pdf>.
- ³ http://www.brainresource.com/uploads/BRC_PersonalMedDetail_Apr04.pdf
- ⁴ There has been a myriad of new supporters – for example BRC is one of more than 100 members of the PersonalizedMedicineCoalition, the lead industry representative group.
- ⁵ <http://www.cms.hhs.gov/NationalHealthExpendData/downloads/proj2006.pdf>
- ⁶ Pharma 2020: The Vision - <http://www.pwc.com>
- ⁷ Wall Street Journal November 1, 2007, Drug Drought Deepens, Posted by Scott Hensley
- ⁸ Wall Street Journal Oct 10, Meter Set to Run on J&J's Cash-Back Deal, Posted by Peter Loftus
- ⁹ T. J. Moore, M. R. Cohen, C. D. Furberg: Serious Adverse Drug Events Reported to the Food and Drug Administration, 1998-2005. *Arch Intern Med* 167 1752-1759 (2007). The five painkillers causing death were: Oxycontin, Fentanyl, Morphine, Acetaminophen and Methadone and the antipsychotic is Clozapine. The nonfatal drugs were Estrogens, Insulin, Interferon beta (MS/Cancer), Paroxetine (Depression), Clozapine (Schizophrenia), Oxycontin, Warfarin (anti clotting agent) and Fentanyl.
- ¹⁰ Presentation in November 1998 by Dan Segal to Telstra Corporation senior management.
- ¹¹ Sourced from a Presentation by Mikael Edholm in November 2000 (www.predicom.com)
- ¹² *Forbes ASAP* - December 1, 1995.
- ¹³ Chris Anderson, *The Long Tail*, Hyperion (2006)
- ¹⁴ Dan Segal was an equities telecommunications analyst for Salomon Smith Barney/Citigroup through the major part of the 1990's.
- ¹⁵ Moore's Law: the number of transistors that can be placed on an integrated circuit doubles every two years, this observation by Intel co-founder Gordon Moore in 1965 has held since.
- ¹⁶ Metcalfe's Law: the value of a telecommunications network is proportional to the square of the number of users of the system, Robert Metcalfe.
- ¹⁷ Taken from a Presentation by Mikael Edholm, data from Bureau of Economic Analysis 1997/8.
- ¹⁸ Department of Health and Human Services, US System of Oversight of Genetic Testing: A response to the Charge of the Secretary of HHS (November 2007)
- ¹⁹ M. Chicurel: Databasing the brain. *Nature* 406 822 (2000).
- ²⁰ Federal Communications Commission, Digital Tornado: The Internet and Telecommunications Policy, March 1997.
- ²¹ See for example the websites of Affymetrix and Illumina for more detail.
- ²² Taken from a W Frueh FDA presentation based on Hillman MA, Wilke RA, Caldwell MD, Berg RL, Glurich I, Burmester JK: Relative impact of covariates in prescribing Warfarin. *Pharmacogenetics* 14(8) 539-47 (2004).
- ²³ The Wellcome Trust Case Control Consortium: Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* Vol 447 1038 (2007)
- ²⁴ CT Dollery: Beyond Genomics. *Nature* 82 4 (2007)
- ²⁵ See reference 2.
- ²⁶ D. Williams, J. Seus: Medical Tourism: Implications for participants in the US Health Care system www.medtripinfo.com.
- ²⁷ A. McWilliam, R. Lutter and C. Nardinelli: Health Care Savings from Personalizing Medicine Using Genetic Testing: The Case of Warfarin, AEI-Brookings Joint Center for Regulatory Studies Working Paper 06-23 November 2006. Range in savings of between \$100 million to \$2 billion, depending on assumptions over the number of adverse affects avoided though genetics testing.
- ²⁸ Assumptions included: genetic testing allowing 85,000 users to avoid bleeding events and 17,000 strokes annually, direct costs of \$39,500 per stroke, direct costs of bleeding \$13,500, costs of genetic testing of about \$700 million (2 million tests x \$350 per test). Net savings made up of \$1.15bn in reduced bleeding costs, \$675m in reduced stoke costs, \$700m testing costs.
- ²⁹ See Reference 2.
- ³⁰ Slide taken from a 2005 presentation by W. Frueh, FDA: Personalized Medicine: What Is It? How Will It Affect Health Care.

BrainResource – Personalized Medicine 2007 Update

³¹ M. Trusheim, E. Berendt and F. Douglas: Stratified Medicine. *Nature Reviews* 6 (2007)

³² US Department of Health and Human Services: *Personalized Health Care: Opportunities, Pathways, Resources* (2007).

³³ Peter Lawson, Diagnosing Diagnostics, Thomas Weisel Partners Equity Research (2007).

³⁴ Please note earlier comment that BrainResource retains a significant interest (by way of licence) in the intellectual property created under iSPOT as opposed to the entirety.

³⁵ Benjamin Graham, Security Analysis (1934): "Unseasoned companies in new fields of activities... provide no sound basis for the determination of intrinsic value... Analysts serve their discipline best by identifying such companies as highly speculative and not attempting to value them... The buyer of such securities is not making an investment, but a bet on a new technology, a new market, a new service... Winning bets on such situations can produce very rich rewards, but they are in an odds-setting rather than a valuation process."

³⁶ PhRMA and <http://www.imshealth.com/>.

³⁷ PhRMA, Mental Illness Report (2006).