

Impact of Personalized Medicine MDx tests on
Oncology Therapeutics
By Scientia Advisors

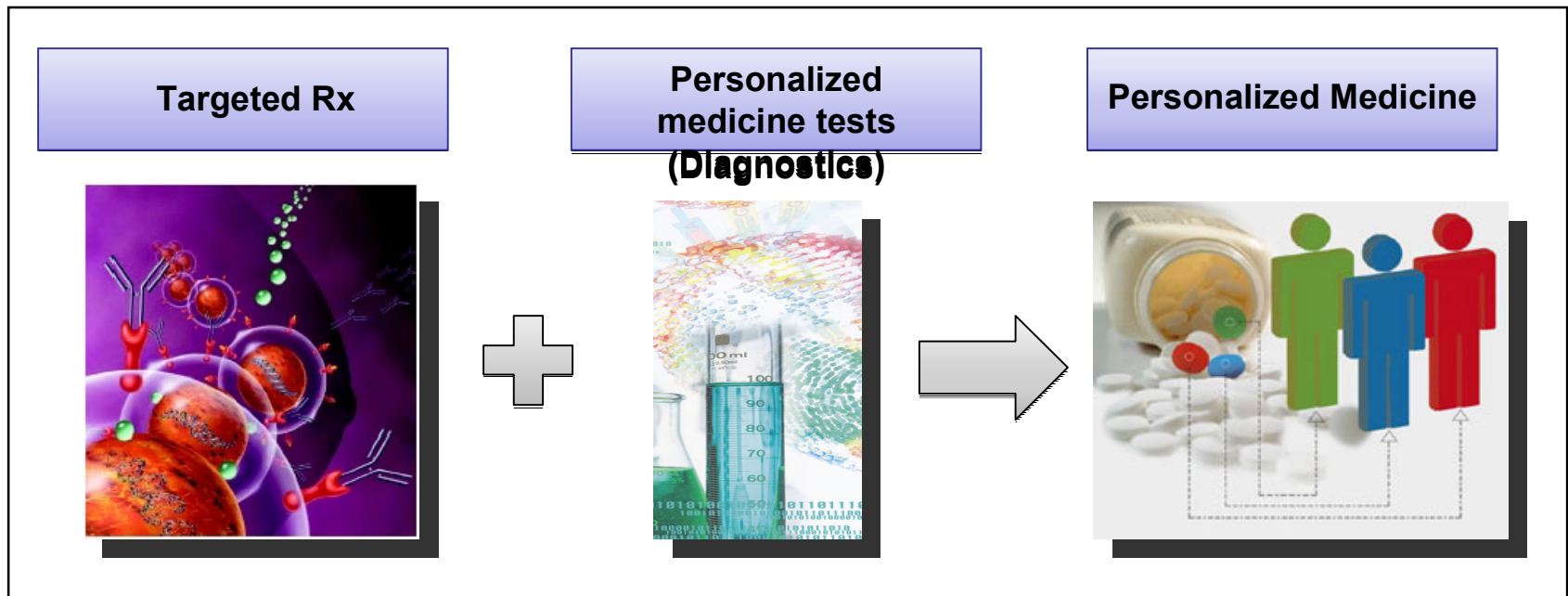
Scientia Advisors LLC
1 Broadway, 14th Floor
Kendall Square
Cambridge, MA 02142
www.scientiaadv.com

2007
Scientia Advisors, LLC
Boston ■ Palo Alto

- Dx = *In vitro* Diagnostics
- MDx = Molecular Diagnostics
- Rx = Therapeutics
- SNP = Single Nucleotide Polymorphism
- Thx = Theranostics
- WW = Worldwide

The Right Therapy for the Right Patient, at the Right Time

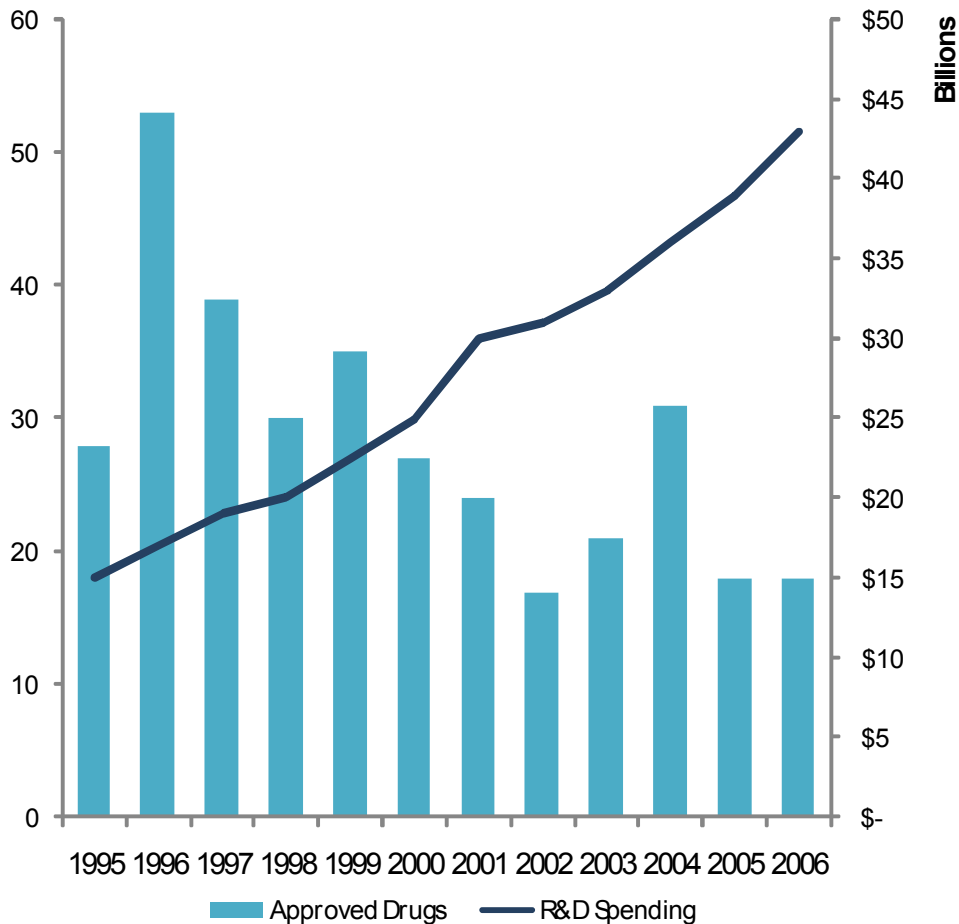
Best responders to therapy identified using Personalized Medicine Tests and then given the Targeted Rx at the right time to maximize efficacy and minimize adverse reaction



- Overview of Oncology Rx
- Overview of personalized medicine tests
 - » Early Detection
 - » Prognosis
 - » Theranostics (Thx)
- Conclusion

Fewer drug approvals & impending patent expirations plague Pharma's prognosis

Combination with personalized medicine tests could be one way to reinvigorate the industry



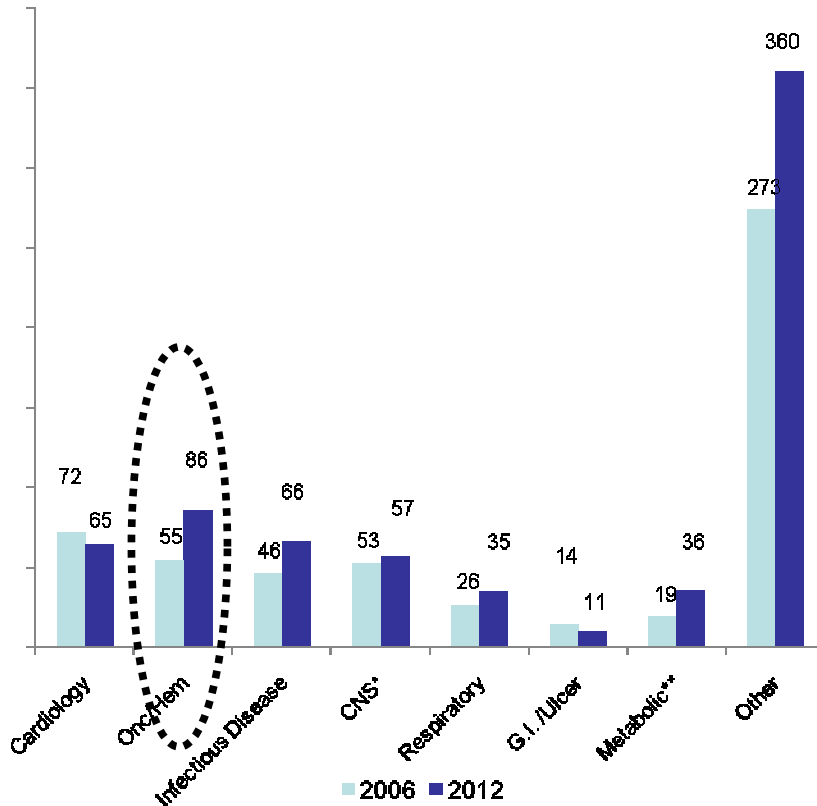
Source: Scientia Analysis; Wall Street Journal "Big Pharma Faces Grim Prognosis"; PharmaVoice, RPM report

Key Takeaways

- Pharma has not had much luck with new products
 - » R&D spending is increasing as number of molecules approved are decreasing
 - » Fewer molecules are submitted to the FDA for approval every year
 - » An increasing number of molecules are going off patent
- *"Personalized Medicine already is impacting the basic information we have about new drugs and the patients who take them. This will steadily increase, becoming the background information for every new drug."*
– Dr. Brian Spear, Abbott
- *"Approaches like personalized medicine tests that get drugs to the right patient, while predicting toxicity and ensuring patient compliance is going to be a tremendous help to the industry."*
– Dr. Peter Corr, Pfizer

Oncology Rx is one of the most attractive areas in therapeutics...

WW Drug sales by therapeutic area (\$B)



* Includes Alzheimer's, Epilepsy and Head Trauma

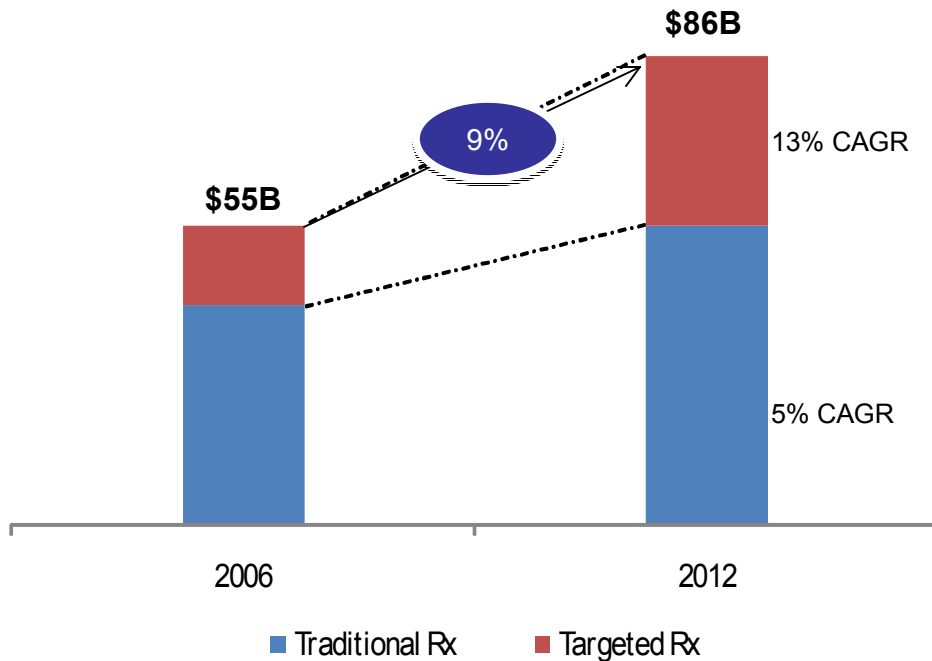
** Includes Diabetes and Obesity

Key Takeaways

- Total Rx sales in 2006 was ~\$560B growing at 15+% CAGR
- Cardiology Rx sales are predicted to fall '06-'12 with a CAGR of -2%, due to the introduction of generic versions of existing therapeutics, and newer therapies needing a few more years in the development phase
- Metabolic Disease Rx is the fastest growing sector with a high CAGR in both Diabetes and Obesity Rx sales (11% and 22% respectively)
- Infectious disease Rx increases at a moderate rate due to newer quinolones and antivirals
- Oncology Rx is one of the faster growing sectors in Rx sales (9% CAGR '06-'12); driven by targeted Rx

... And is most likely to be influenced by personalized medicine

Targeted oncology Rx has a higher CAGR as compared to traditional oncology Rx

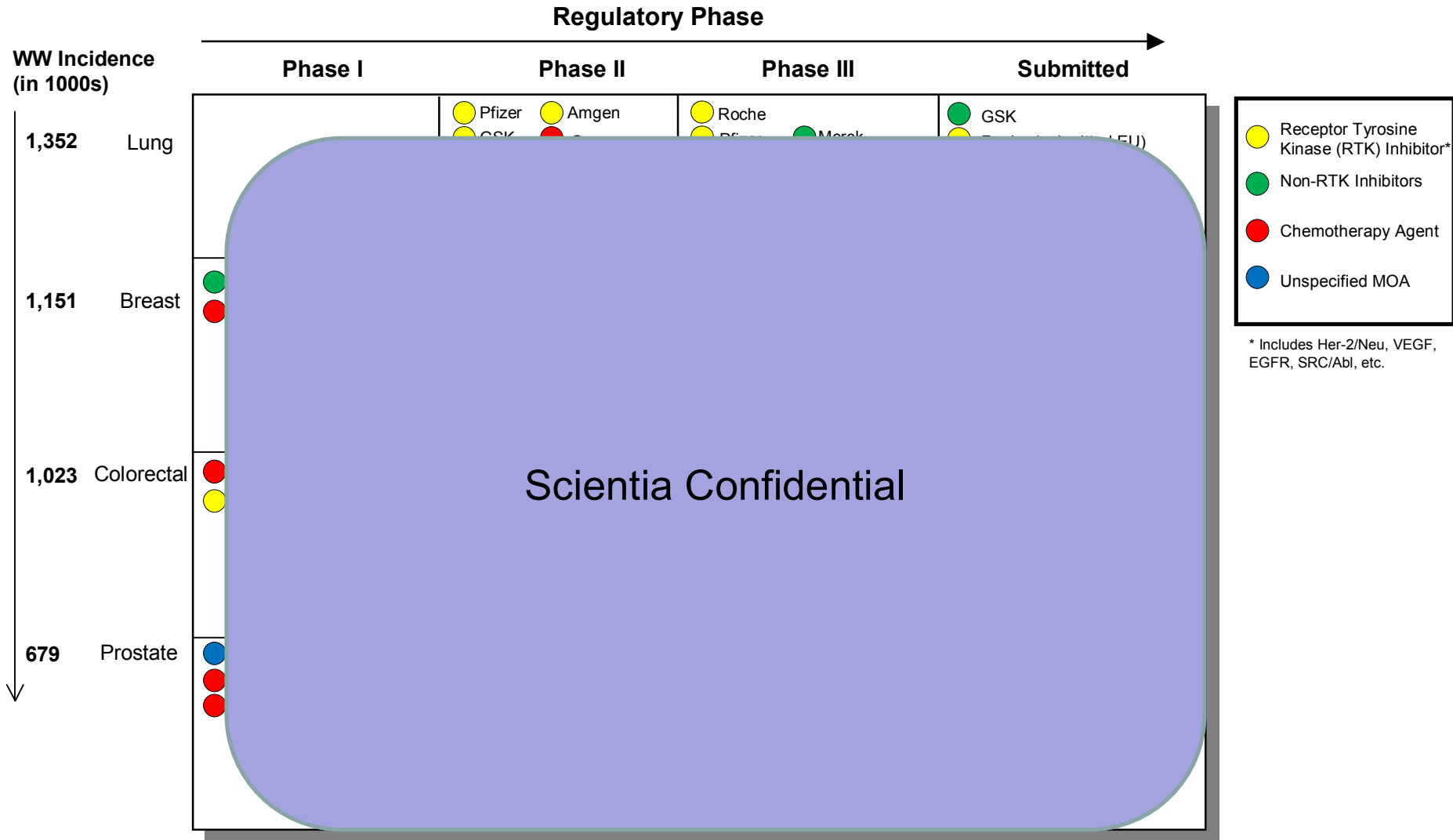


Source: Scientia analysis, 2007 Cowen report on therapeutics

Key Takeaways

- Targeted oncology Rx have a higher growth potential than traditional oncology Rx
- Thousands of cancer patients are already benefiting from several targeted Rx such as Avastin and Gleevec, personalized medicine tests will enhance the safety and efficacy of these targeted Rx
- Targeted oncology Rx are most likely to be influenced by personalized medicine tests
 - » Example: BCR/ABL test enhances the efficacy of Gleevec
 - » Example: UGT1A1 test improves the safety of Irinotecan
- High growth potential of targeted Rx will in turn drive the growth of personalized medicine tests
- In addition to oncology, infectious disease Rx such as HIV Rx have also readily adopted personalized medicine tests (e.g. HIV viral load, resistance tests)

Pharma oncology pipeline: Increased prevalence of targeted therapeutics which will in turn drive the growth of personalized medicine tests

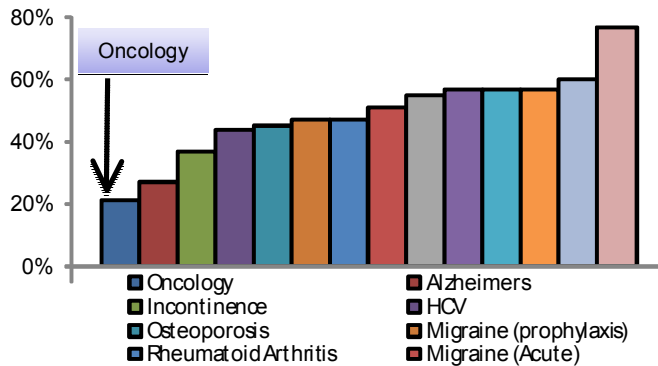


Source: Scientia Analysis; SG Cowen & Co Report; Company Websites; ClinicalTrials.gov

Plagued by low efficacy & safety; Oncology Rx will be one of the chief adopters of personalized medicine tests

Oncology Rx problem: low efficacy & safety

Oncology Rx have low efficacy



Oncology Rx have low safety profile

"Cancer Rx, Fentoral is tied to several deaths"

"London Cancer Rx Trial Goes Horribly Wrong"

"Smart cancer Rx Sunitinib may have toxic effects on heart"

"FDA severely limits access to cancer drug Iressa"

Current Oncology Rx unmet needs

- 50% of oncology Rx are not as efficacious for the entire population as prescribed
- Oncology Rx has the lowest efficacy compared to other Rx
 - » Historically, oncology compounds tend to have a significantly lower success rate in clinical development than compounds in other areas, such as cardiovascular disease

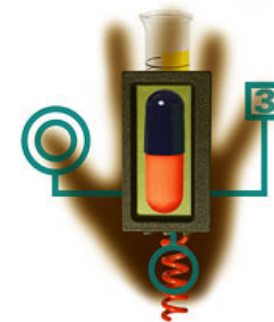
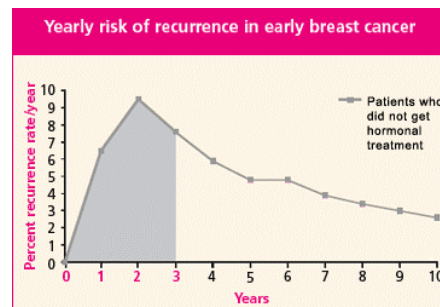
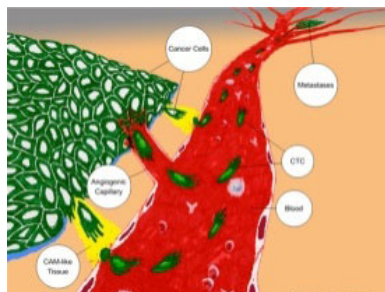
Solution: Personalized medicine tests

- Fewer rates of adverse reactions
- Better response to Rx, with correct dosages
- Rx provided only when necessary; leading to reduced healthcare costs
- Faster approval of drugs, with smaller test population, in shorter period
- Faster rate of R&D with improved drug discovery targets
- Revival of drugs that failed in the past

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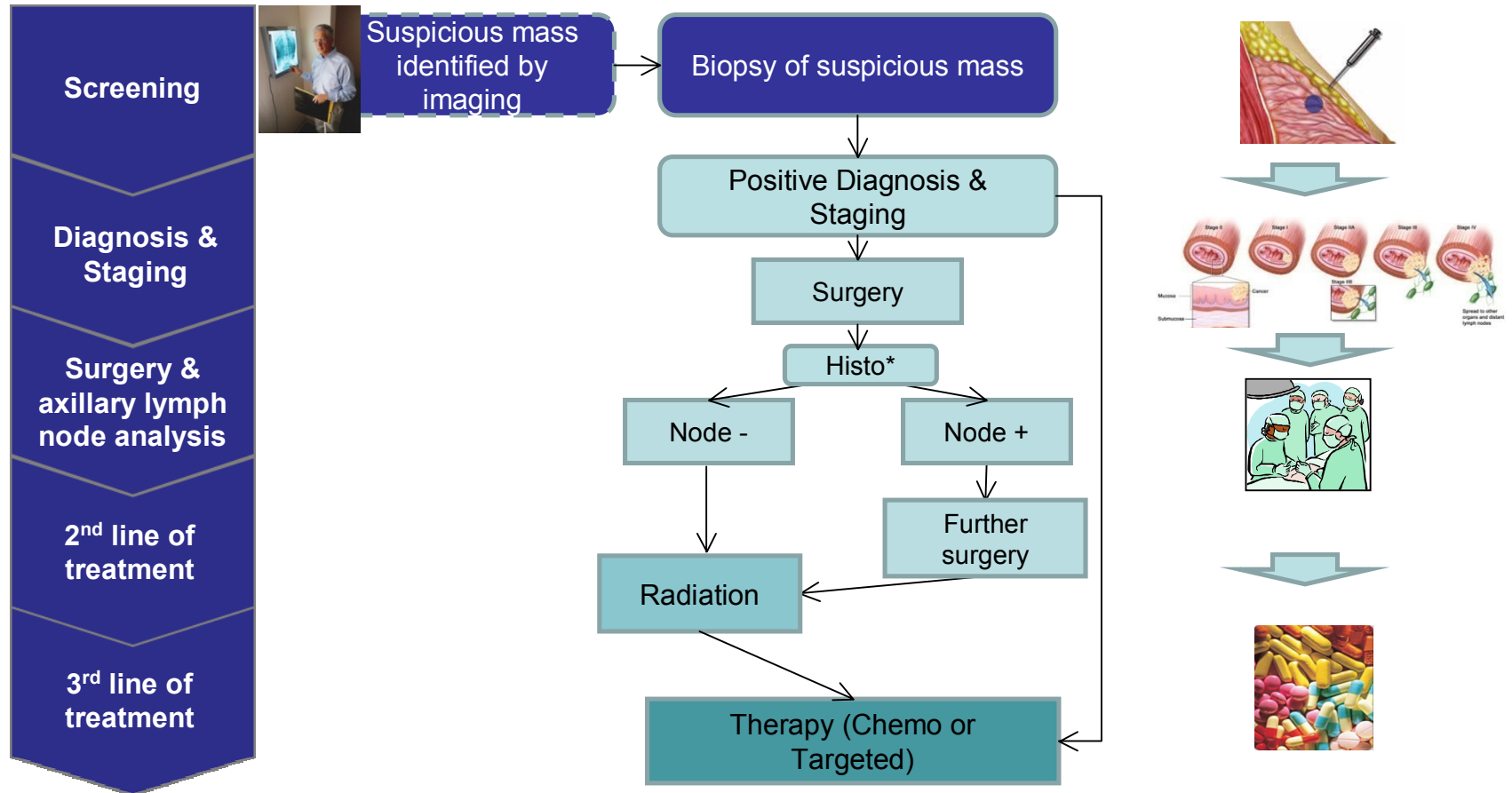
- Definition:

MDx personalized medicine tests include early detection tests that enable early and accurate detection of disease, prognosis tests that provide disease recurrence free survival information, and theranostics tests that enable increased treatment efficacy and reduced adverse events



Overall cancer care cycle

Most solid tumors^ follow a fairly standard patient care cycle



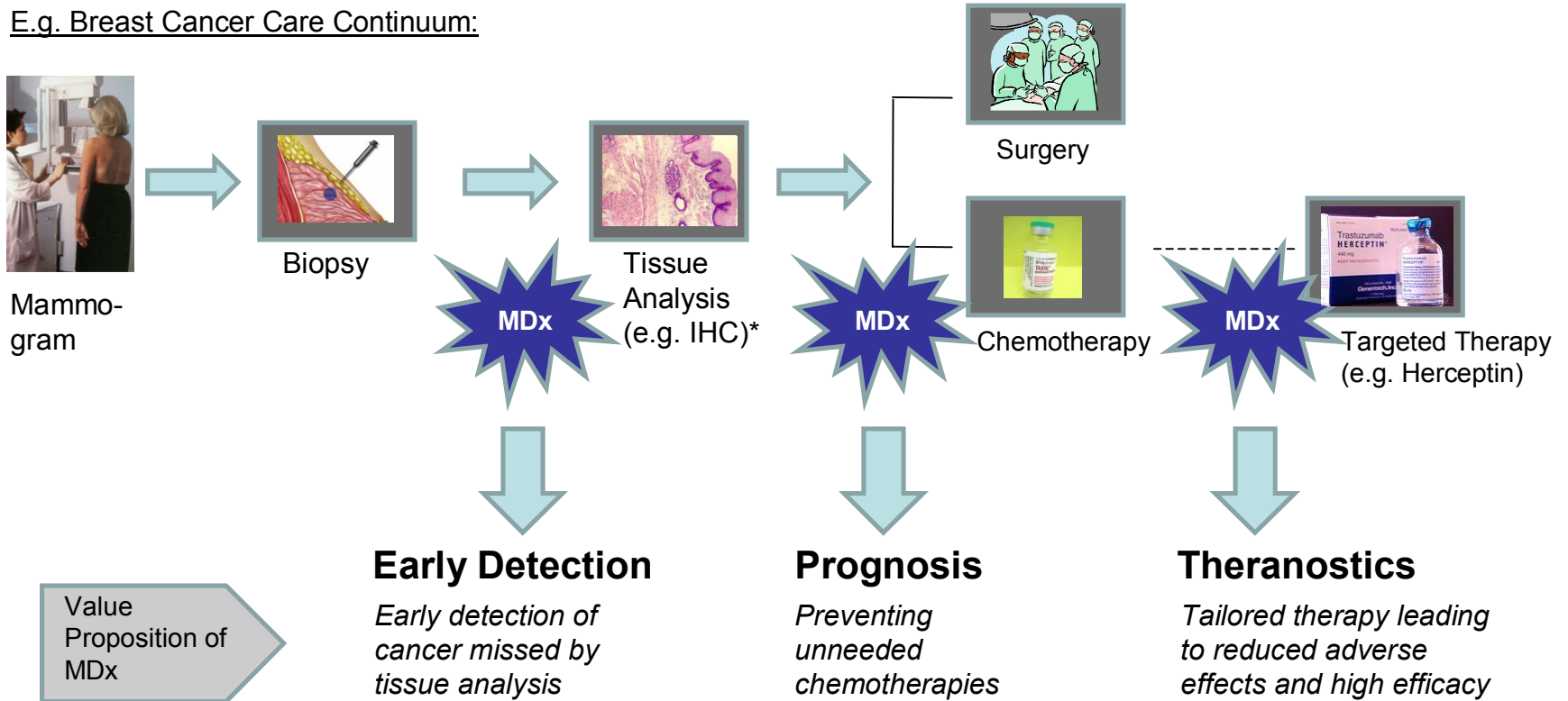
- First line of treatment
- Second line of treatment
- Third line of treatment

* Histology

^ excludes Hematopoietic tumors such as leukemia and lymphoma

E.g. The breast cancer patient care continuum has been enhanced by MDx personalized medicine tests

E.g. Breast Cancer Care Continuum:



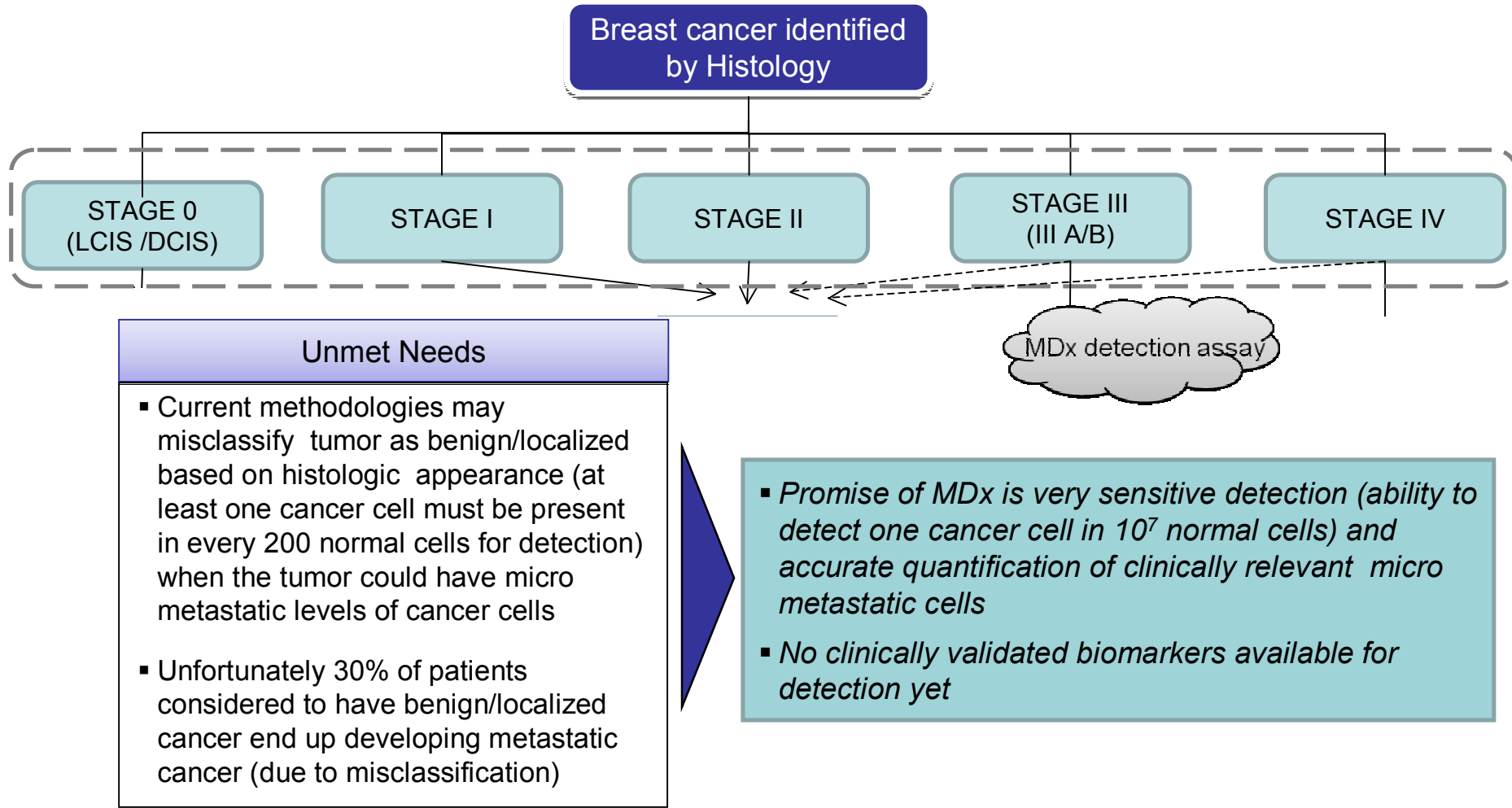
- MDx based early detection will dramatically increase the use of Rx and bundling with early detection tests will give pharma an opportunity to allow Rx to be introduced earlier in the cancer care paradigm
- The use of MDx in prognosis will reduce unnecessary therapies; thus reducing healthcare costs
- The use of MDx theranostics will lead to better drugs that can in turn command premium price
- The breast cancer care cycle of MDx personalized medicine is almost complete; Scientia believes that lung and colorectal cancer will follow suit

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- Detection of cancer is currently done using Pathology
 - » Based on an optical method of detection
 - » Only detects one cancer cell in 200 normal cells
 - » Can lead to mis-classification of tumors
- MDx personalized medicine test will improve the detection/staging of Cancer
 - » More sensitive than optical methods of detection, can detect one cancer cell in 10 million normal cells; leading to earlier detection of cancer
 - » More accurate classification of tumors
 - » Early cancer detection will not only lead to increased patient population implying higher oncology Rx sales, but will also give pharmaceutical companies access to a wider range of patients at an earlier point of the cancer care paradigm

Breast cancer detection

Today's detection methods (Histology) may miss micro metastatic levels of cancer leading to poor prediction of disease outcome and treatment



Source: Scientia analysis, J Am. Surg "Molecular detection of breast cancer", NEJM "Molecular classification of breast cancer"

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Prognosis

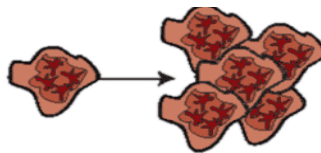
A reduction in unnecessary therapies; thus reducing healthcare costs

- Predicts aggressiveness of cancer, which was not possible by traditional pathology methods, thus addresses an unmet need in oncology today
- Identifies patients with high risk of recurrence who may benefit from adjuvant chemotherapy (improved recurrence-free and overall survival)
- Applies only to early stage patients with inherently good chances of survival (who may be cured with local/regional therapy alone)
- Will reduce unnecessary chemotherapies, leading to fewer adverse side effects
- Are not theranostic tests, but influence key therapy decisions



DNA Mutation

Mutation inactivates tumor suppressor gene



Uncontrolled Cell Growth

Mutation inactivates DNA repair gene and several more tumor suppressor genes



Metastasis

Transfer from one organ or part to another organ or part not directly connected with it

Prognosis^ tests are high value* diagnostics that reduce healthcare expenditure

e.g. Oncotype Dx from Genomic Health

Key Features

- Predicts likelihood of recurrence and benefit of chemotherapy for early stage (N- ER+) breast cancer
- Test based on algorithm and proprietary 21-gene panel using quantitative RT-PCR
- Genomic Health Financials:
 - ~\$25M Revenue 2006, \$120M expected by 2008
 - \$3,460 price per test

* Provide critical information that helps physicians make clinically relevant decisions; as a result command premium prices

Source: Scientia Analysis; Genomic Health company financials

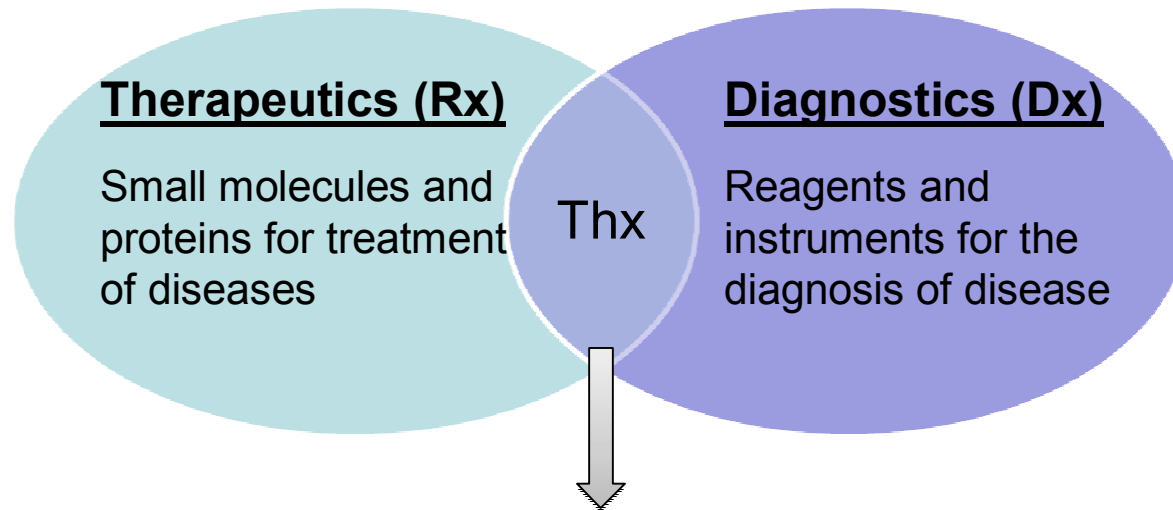
Drivers of Success

- 7 studies with over 2600 patients, published in peer-reviewed journals and presented at national meetings validate the correlation between test results and the need for chemotherapy
- Studies have been conducted with Kaiser Permanente to show economic benefit
- Sales modeled around sales for big pharmaceutical companies, with clinical validation to help secure reimbursement

- Increasing adoption and reimbursement
 - » Over 27,000 tests have been ordered by over 5,500 Physicians since 2004
 - » Approximately 80% of the population is covered for the test

^ Other breast cancer prognosis tests provided by Agendia, ABT-CRA, Ipsogen, Exagen, Aviara; with Veridex (JnJ) and Roche entering the market in the future

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Theranostics (Thx) are therapy specific diagnostics that can be used to select patients for treatments that are particularly likely to benefit them and to minimize side-effects.

Thx can also provide an early and objective indication of treatment efficacy in individual patients, so that (if necessary) the treatment can be altered with minimum delay.

The two types of theranostic tests

Both are essential for improved outcomes

Theranostic Tests

Adverse Drug Reaction Tests

- These tests identify people likely to have adverse drug reactions to particular drugs, reducing the number of people reporting side effects
- Adverse Drug Reactions is the 6th leading cause of death
- These are one-time tests that cost between \$300 and \$800.
- E.g. CYP 450 test, UGT1A1 tests

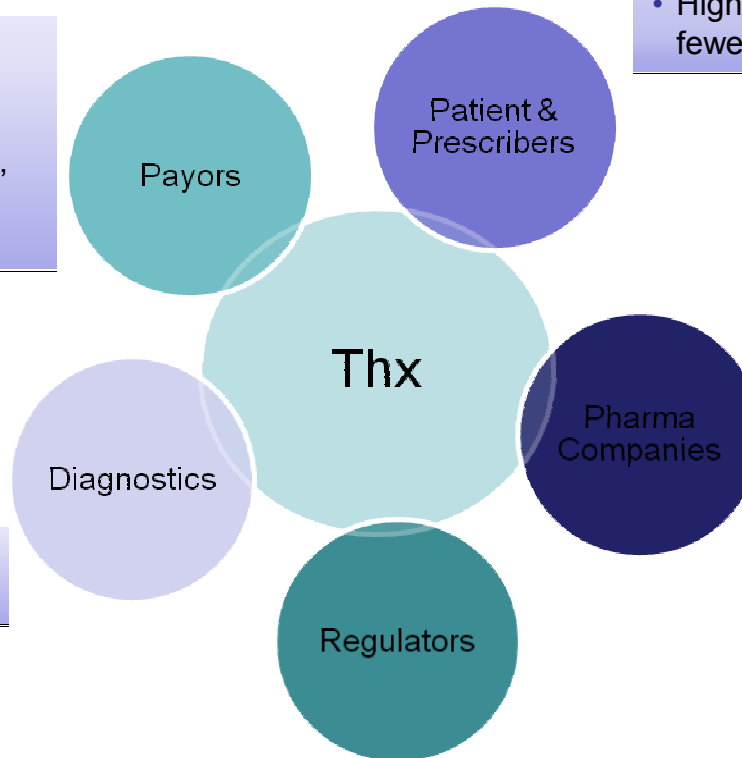
Drug Responder Category Tests

- These tests distinguish between responders and non- responders to a specific drug or set of drugs
- When combined with the adverse reaction tests, they can provide a comprehensive response profile, which can be used for treatment decisions
- E.g. Her2/Neu test, BCR/ABL test

Theranostics provides clear cost-to-benefit ratios and quality-of-life payoffs for all stakeholders of healthcare

- Clinical utility changes medical practice increasing payers' willingness to pay
- When paired with Dx test results, more efficient payment decision

- Guides Rx decisions
- Higher efficacy of treatment, with fewer adverse side effects



- Increase in Dx volume and revenue

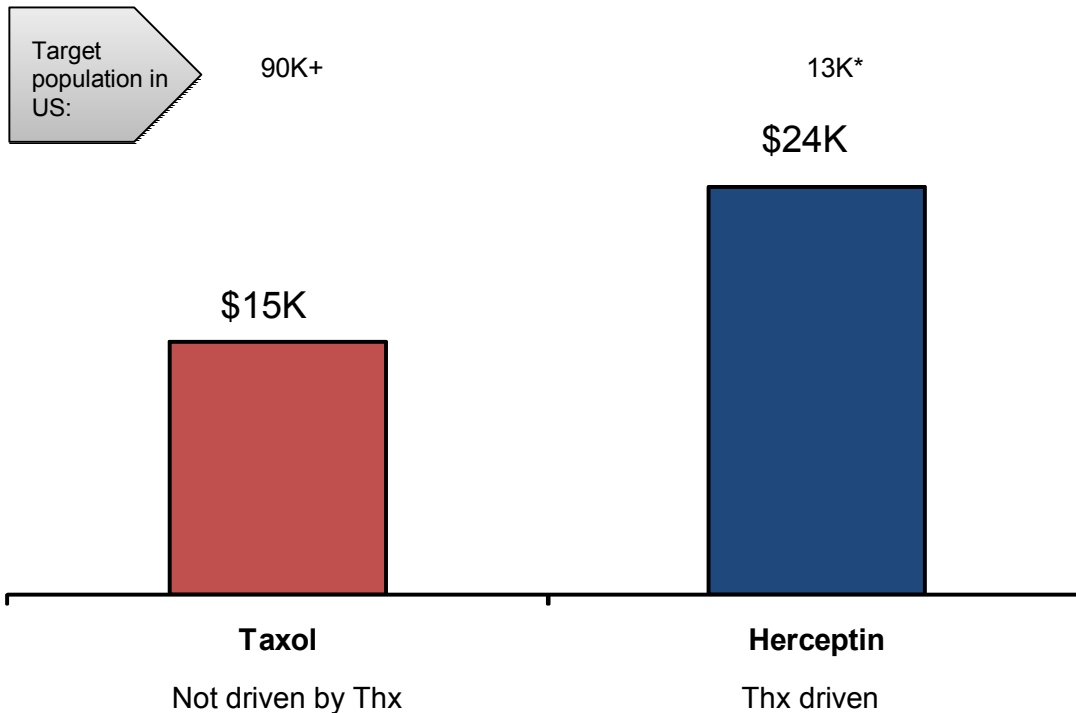
- Potential for higher pricing due to higher efficacy
- Enables focused trials – smaller group for shorter periods with better results

- Faster approval process due to focused trials

Source: Scientia Analysis

Therapies accompanied by Thx command a premium price in the market

Thx driven Rx command premium pricing over traditional Rx...



...as they promise:

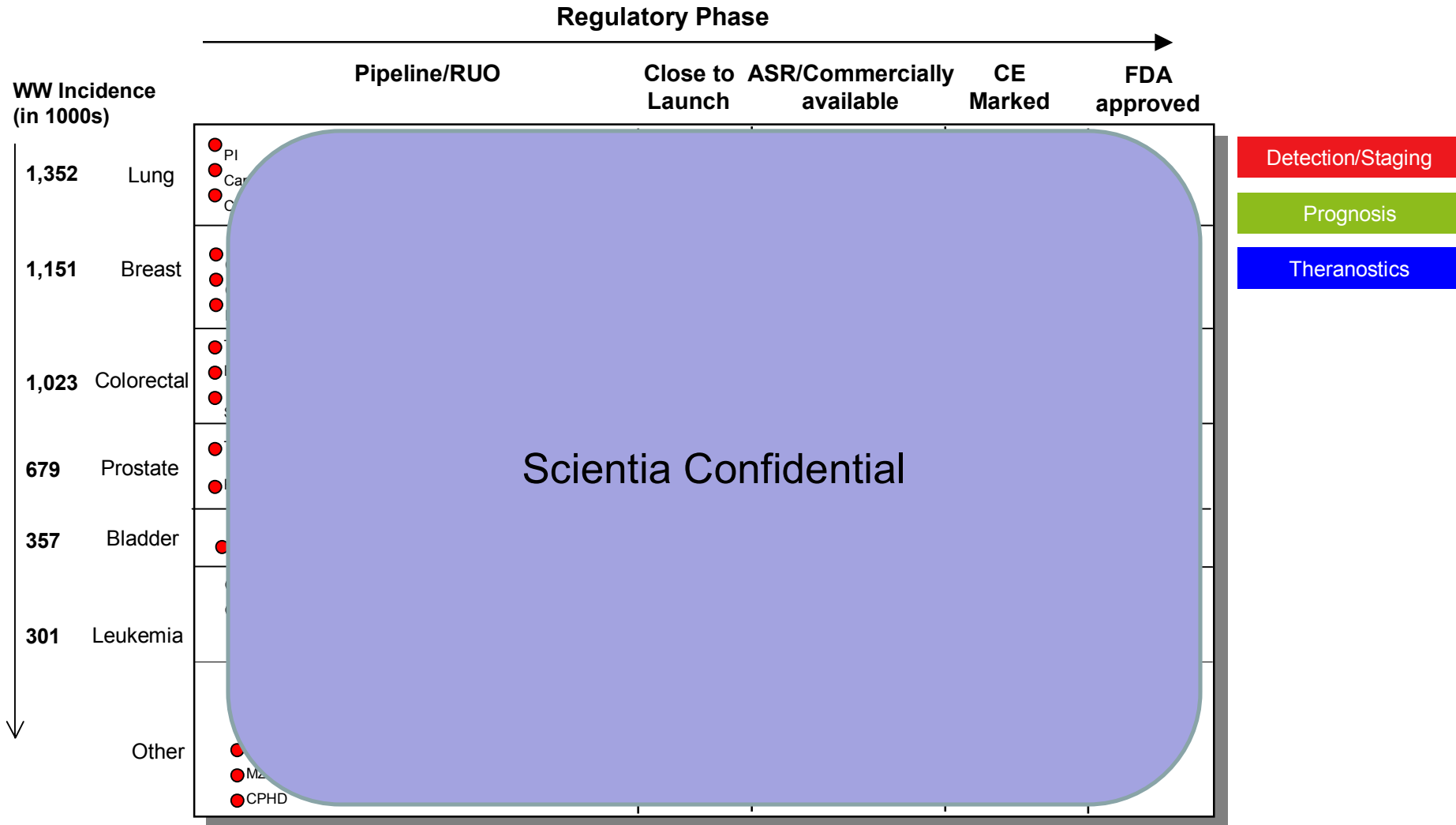
- **High efficacy:** Herceptin showed that it reduced the risk of recurrence by as much as 52%.
- **Reduced adverse events by excluding non-responders:** Adverse events cause >2 million hospitalizations today with a cost of \$100 billion to the healthcare system

Source: Scientia Analysis; 2003 Commerzbank report on Roche "Tamoxifen Breast Cancer Prevention Has Small Mortality Effect"; Drugs.com; Roche corporate presentation; Genentech

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The overall MDx personalized medicine landscape

Numerous players emerging with novel biomarkers



Source: Scientia analysis

FDA and payors are pushing for integration of Rx with personalized medicine tests



On Dec. 24 2004, the FDA approved AmpliChip CYP450 test, the first FDA approved PGx test



On Aug. 22 2006, the FDA approved UGT1A1 test, for use in identifying patients that may be at increased risk of adverse reactions to irinotecan HCl



mammaprint™

On Feb. 6 2007, the FDA approved Agendia's MammaPrint Dx for breast cancer recurrence, the first IVDMIA test



Payors reimburse Genomic Health's OncoType Dx assay for breast cancer recurrence



On Sept. 18, 2007 the FDA approved the first genetic test for Warfarin sensitivity, "Verigene"



On Dec. 12, 2007 the FDA relabeled Carbamazepine to Include Recommendation of Genetic Test for Patients with Asian Ancestry

Case studies on pharma's perception of integrated personalized medicine tests

Roche appears to be the only Pharma with integrated Rx-Dx offering

Rx-Dx Collaborations



- Collaboration with Abbott/Vysis and DakoCytomation for Her2/Neu testing for Herceptin (first FDA approved Thx)



- Collaboration with Genzyme genetics BCR/ABL testing for chronic myeloid leukemia (CML) Rx



- Collaboration with Monogram Biosciences for HIV drugs
 - » Monogram's Trofile Assay is used to test CCR5 which is instrumental in the decision to administer Pfizer's recently approved Maraviroc



- Collaborated with University of North Carolina at Chapel Hill for breast cancer studies on Gemzar. Lilly used a breast cancer prognosis test that predicts need for Gemzar in early stage breast cancer patients

Integrated Rx and Dx Divisions



- Integrated Rx/Dx: close cooperation between Rx and Dx to validate novel Oncology markers for personalized medicine tests



- Partial Control with limited Rx/Dx integration (Abbott Dx & Vysis)



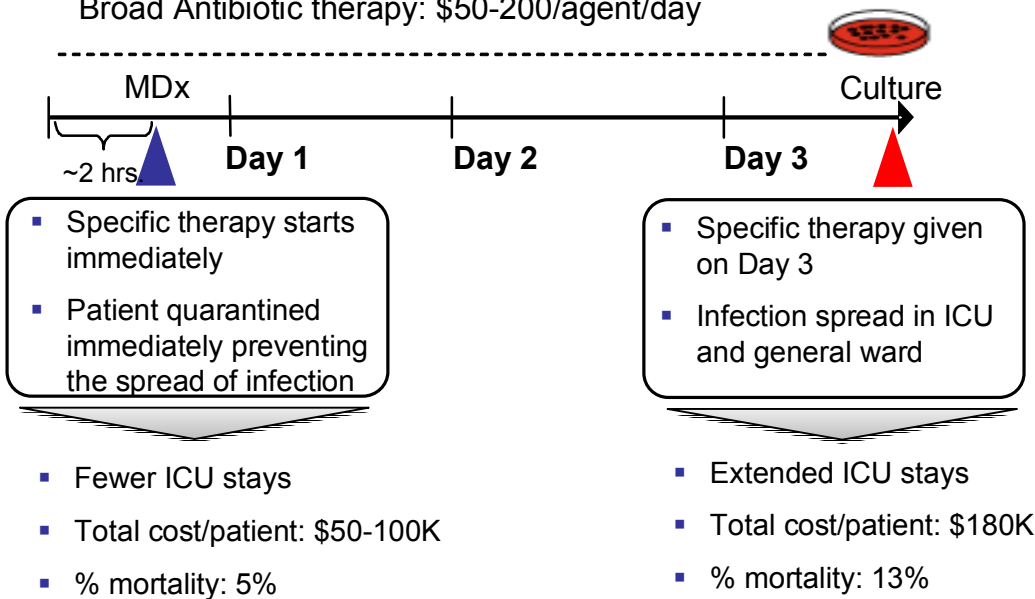
- Partial Control with limited Rx/Dx integration (Veridex and Ortho Clinical Diagnostics)

Source: Scientia Analysis; Company Corporate Presentations; Press Releases

By providing early diagnosis, MDx is enabling the delivery of right therapy at the right time

Sepsis Causing Pathogens Example:

Broad Antibiotic therapy: \$50-200/agent/day



"My top of mind issue is early and accurate diagnosis..I only get information from Pharma on therapy but I wish someone could educate me about early diagnosis using MDx to enable delivery of right therapy at the right time"
- ICU physician, Methodist hospital

Key Take-Aways

- Historically, in critical care infectious diseases such as sepsis, ICU[^] physicians have to wait 2-3 days to get accurate information about specific pathogens in patient samples. With the introduction of MDx tests, results would be available in about 6 hours, thus ICU[^] stays will be shortened; reducing costs and associated risks for the patients
- Hospital acquired infections such as MRSA is a growing healthcare concern; Rx for multi-drug resistant, hospital acquired infection is a major opportunity for pharmaceutical companies
 - » MDx is facilitating this opportunity by enabling the early detection of these pathogens
 - » Pfizer's Zyvox is the only IV/Oral MRSA Agent; however Zyvox is plagued by safety concerns associated with intravascular catheter infections
- MDx provides early diagnosis; thus enabling the delivery of right therapy at the right time

[^]Intensive Care Unit

- Today, Oncology and certain Infectious diseases such as HIV Rx seem to be the first to adopt personalized medicine tests
 - » Personalized medicine tests are likely to become prominent in other therapeutic areas including cardiology, CNS, respiratory, and psychiatric disorders over the next decade
- MDx personalized medicine tests are influencing Rx sales by:
 - » Improving the early detection of cancer, leading to higher Rx sales
 - » Providing a method to predict prognosis of early stage oncology patients, hence helping reduce unnecessary Rx and adverse side effects
 - » Improving efficacy and reducing side effects of targeted therapies
- Changing points of view
 - » Traditionally pharma companies have not looked diagnostic tests as key influencers of Rx sales
 - » While Pharma Companies have taken an initial step toward Personalized Medicine, they need to take a strategic look at how their markets will be impacted by it. Our thesis is that Pharma Companies will be increasingly pressured to control a broader portion of the PharmacoGenomics value chain and to create more efficient processes and discover and validate novel biomarkers

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CONTACT INFORMATION

Harry Glorikian
Managing Partner

hglorikian@scientiaadv.com

Office: +1-617-583-1382

Mobile: 617-407-5093

Fax: +1-617-812-0315

1 Broadway, 14th Floor
Kendall Square
Cambridge, MA 02142

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