Companion Diagnostics for Targeted Cancer Therapies:

Current Trends and Future Directions

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Biomarkers in Diagnostics – Some Definitions

The process by which a biomarker is linked to a clinical significance.

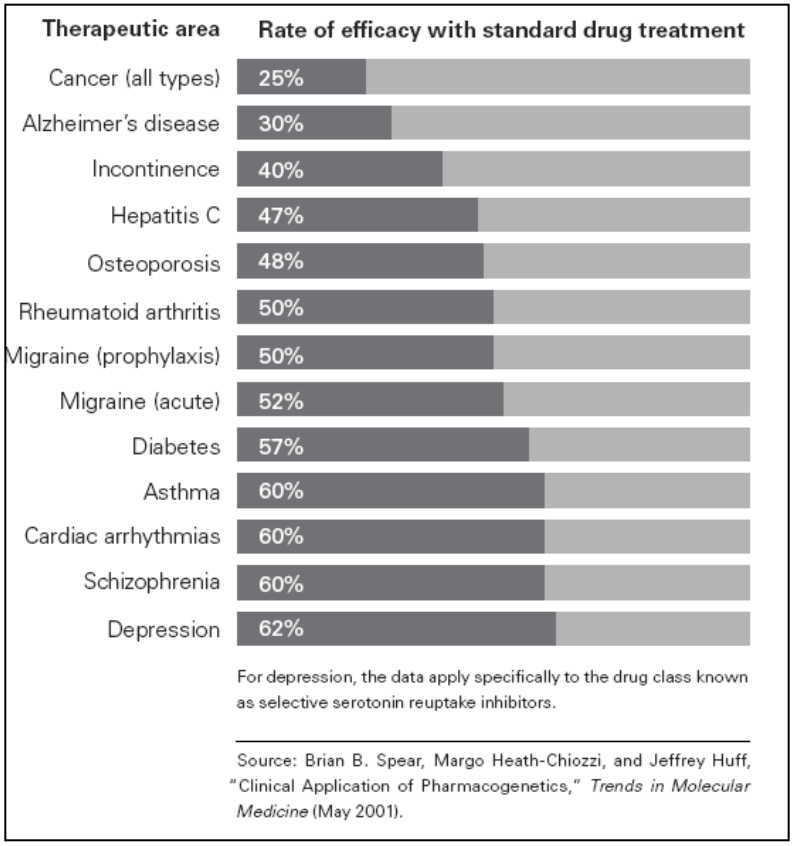
Term	Definition
Exploratory biomarker	An aberrantly expressed or mutated gene, protein, or metabolite that has been associated with a *disease relevant* biological process (i.e. that is amenable to a therapeutic intervention).
Probable valid biomarker	A biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is a *scientific framework* or body of evidence that appears to elucidate the physiologic, toxicologic, or clinical significance of the results.
Known valid biomarker	A biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is *widespread agreement* in the medical or scientific community about the physiologic, toxicologic, or clinical significance of the results.
Companion Diagnostic	A diagnostic test that has been *clinically validated* for use when prescribing a targeted drug therapy.

Source: Clinical Cancer Research 2010, **16**(6)

Objectives

- Describe leading companion diagnostic tests that are gaining traction in the area of oncology
- Learn about strategies for translating research biomarkers to regulated diagnostic tests
- Learn about drug-diagnostic co-development strategies for companion diagnostics

Value Proposition for Companion Diagnostics



Patient stratification to improve drug safety and efficacy:

- Adverse drug reactions are the fourth leading cause of death.
- The cost of adverse drug events has been estimated at $177 billion annually in the U.S.
- Over $350 billion in drug costs are wasted annually due to lack of efficacy.

Source: Personalized Medicine (2011) 8(2), 137-148.

Applications of Companion Diagnostic Testing

Biomarker information on drug labels can describe:

- Drug exposure and clinical response variability
- Risk for adverse events
- Genotype-specific dosing
- Mechanisms of drug action
- Polymorphic drug target and disposition genes

Source: Tufts Center for the Study of Drug Development Impact Report, Dec 2010.

Pharmacogenomic Biomarkers in Drug Labels

*28 in the area of oncology to date**

Drug	Biomarker	Label Sections
Arsenic Trioxide	PML/RARa	Boxed Warning, Clinical Pharmacology, Indications and Usage, Warnings
Busulfan	Ph Chromosome	Clinical Studies
Cetuximab	EGFR, KRAS	Indications and Usage, Warnings and Precautions, Description, Clinical Pharmacology, Clinical Studies
Crizotinib	EML4-ALK	Indications and Usage, Warning and Precautions, Clinical Pharmacology, Clinical Studies, Patient Counseling Information
Dasatinib	Ph Chromosome	Indications and Usage, Clinical Studies, Patient Counseling Information
Erlotinib	EGFR	Clinical Pharmacology
Fulvestrant	ER receptor	Indications and Usage, Patient Counseling Information
Gefitinib	CYP2D6, EGFR	Drug Interactions, Clinical Pharmacology
Imatinib	C-Kit, Ph Chromosome, UGT1A1	Indications and Usage, Dosage and Administration Clinical Pharmacology, Clinical Studies
Lapatinib	Her2/neu	Indications and Usage, Clinical Pharmacology, Patient Counseling Information
Mercaptopurine	TPMT	Dosage and Administration, Contraindications, Precautions, Adverse Reactions, Clinical Pharmacology
Nilotinib	Ph Chromosome, UGT1A1	Indications and Usage, Patient Counseling Information, Dosage and Administration
Panitumumab	EGFR, KRAS	Indications and Usage, Warnings and Precautions, Clinical Pharmacology, Clinical Studies
Rasburicase	G6PD	Boxed Warning, Contraindications
Tamoxifen	ER receptor	Indications and Usage, Precautions, Medication Guide
Thioguanine	TPMT	Dosage and Administration, Precautions, Warnings
Tositumomab	CD20 antigen	Indications and Usage, Clinical Pharmacology
Trastuzumab	Her2/neu	Indications and Usage, Precautions, Clinical Pharmacology
Vemurafenib	BRAF	Indications and Usage, Warning and Precautions, Clinical Pharmacology, Clinical Studies, Patient Counseling Information

Source: FDA website, last updated 8/25/2011

Increased prioritization of biomarkers

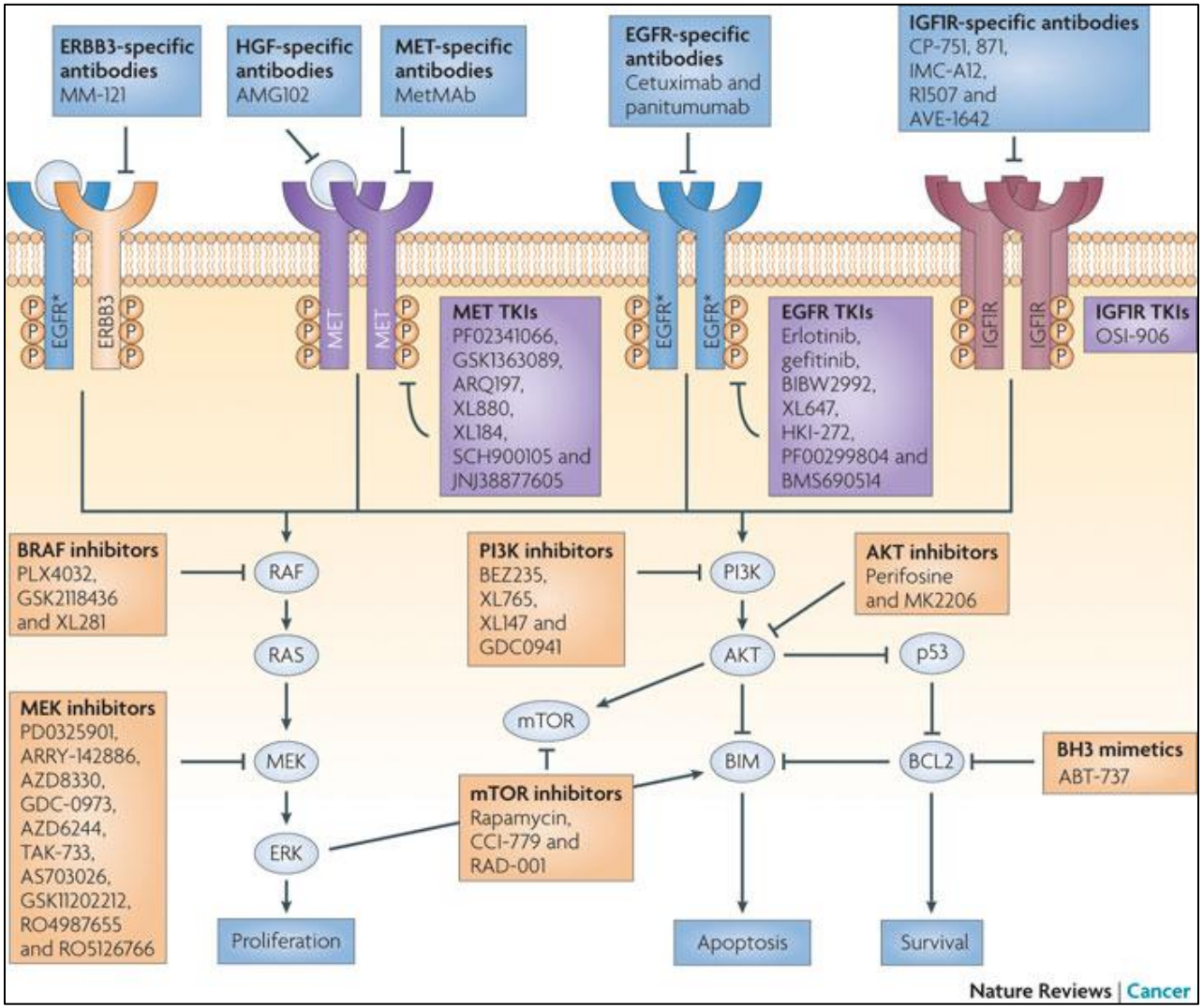
in drug development pipelines

Recent survey of pharmaceutical executives:

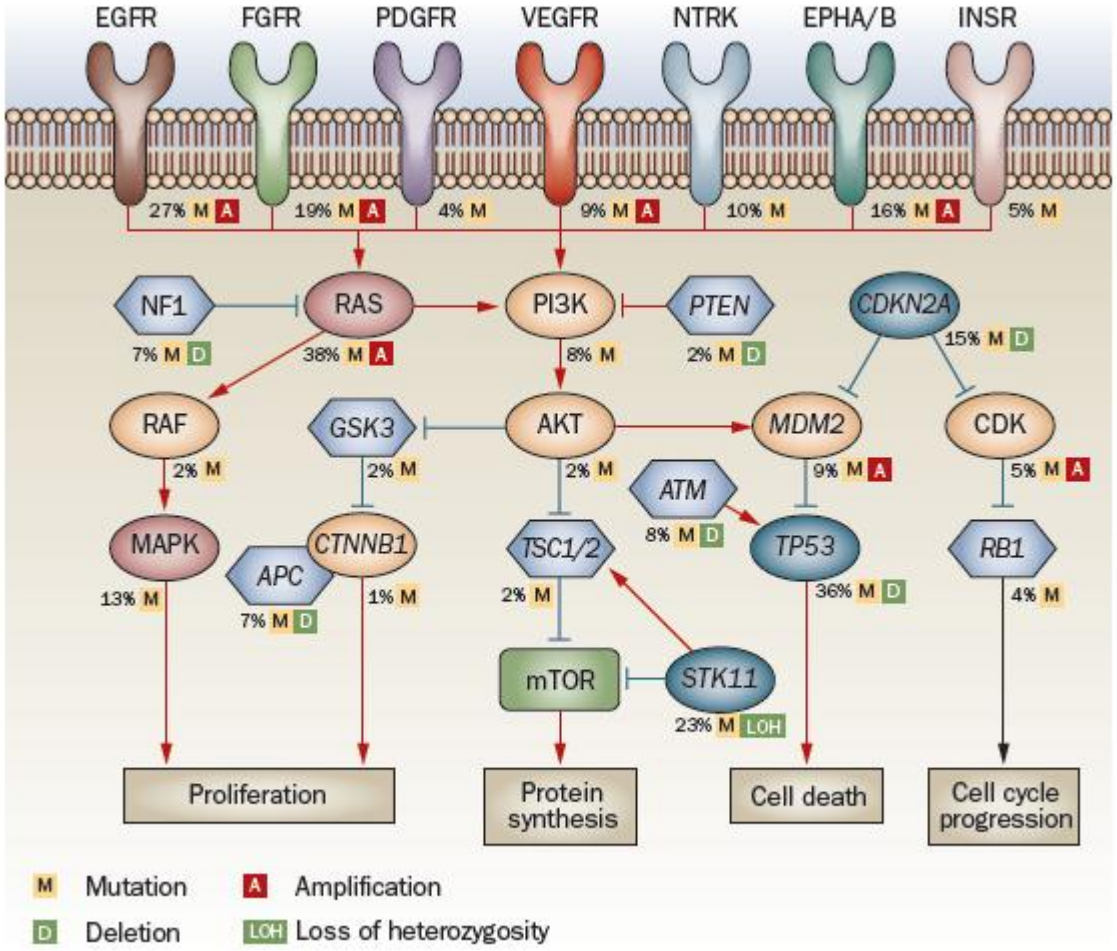
- 100% of respondents reported that they utilize biomarkers when they evaluate compounds in the discovery phase.
- Between 12% and 50% of respondents' drug pipelines are targeted therapies.
- 50% of clinical trials collect DNA from participants to identify biomarkers correlating to drugs' efficacy and safety.
- 10% of the drugs in late-stage clinical trials are expected to have a companion diagnostic.

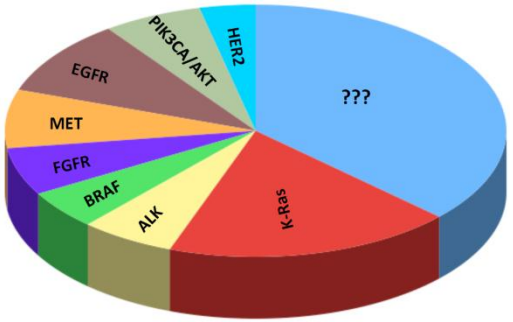
Source: Tufts Center for the Study of Drug Development Impact Report, Dec 2010.

Examples of Targeted Drugs for Cancer Therapy



Disease-Centric Biomarker Strategies: Important Mutated Pathways in Lung Adenocarcinomas





Source: Harris and McCormick, *Nat. Rev. Clin. Oncol.* 7, 251–265 (2010)

…and yet each individual's cancer is uniquely different

Nine Prostate Cancer Genomes (next-generation sequencing)

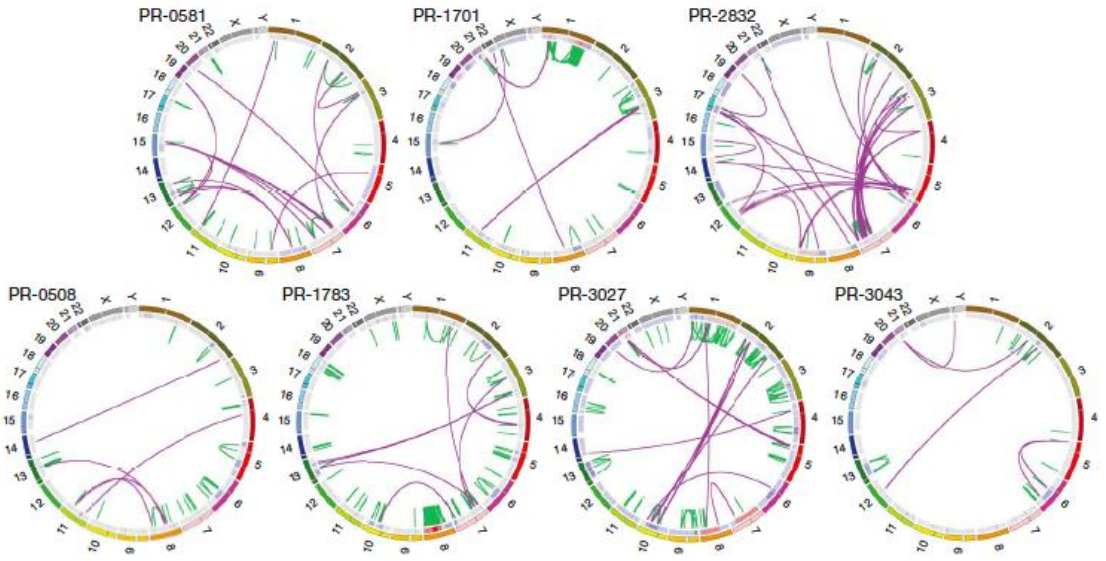


Table 1 | Landscape of somatic alterations in primary human prostate cancers

	Tumour						
	PR-0508	PR-0581*	PR-1701*	PR-1783	PR-2832*	PR-3027	PR-3043
Tumour bases sequenced	97.8×10^9	93.9×10^9	110×10^9	90.9×10^9	106×10^9	93.6×10^9	94.9×10^9
Normal bases sequenced	96.7×10^9	57.8×10^9	108×10^9	92.3×10^9	103×10^9	87.8×10^9	96.6×10^9
Tumour haploid coverage	31.8	30.5	35.8	29.5	34.4	30.4	30.8
Normal haploid coverage	31.4	18.8	34.9	30.0	33.4	28.5	31.4
Callable fraction	0.84	0.83	0.87	0.82	0.84	0.84	0.85
Estimated tumour purity†	0.73	0.60	0.49	0.75	0.59	0.74	0.68
All point mutations (high confidence)	3,898 (1,447)	3,829 (1,430)	3,866 (1,936)	4,503 (2,227)	3,465 (1,831)	5,865 (2,452)	3,192 (1,713)
Non-silent coding mutations (high confidence)	16 (5)	20 (3)	24 (9)	32 (20)	13 (7)	43 (16)	14 (10)
Mutation rate per Mb	0.7	0.7	0.8	1.0	0.8	1.2	0.7
Rearrangements	53	67	90	213	133	156	43

* Harbours *TMPRSS2–ERG* gene fusion

† Estimated from SNP array-derived allele specific copy number levels using the ABSOLUTE algorithm (Supplementary Methods).

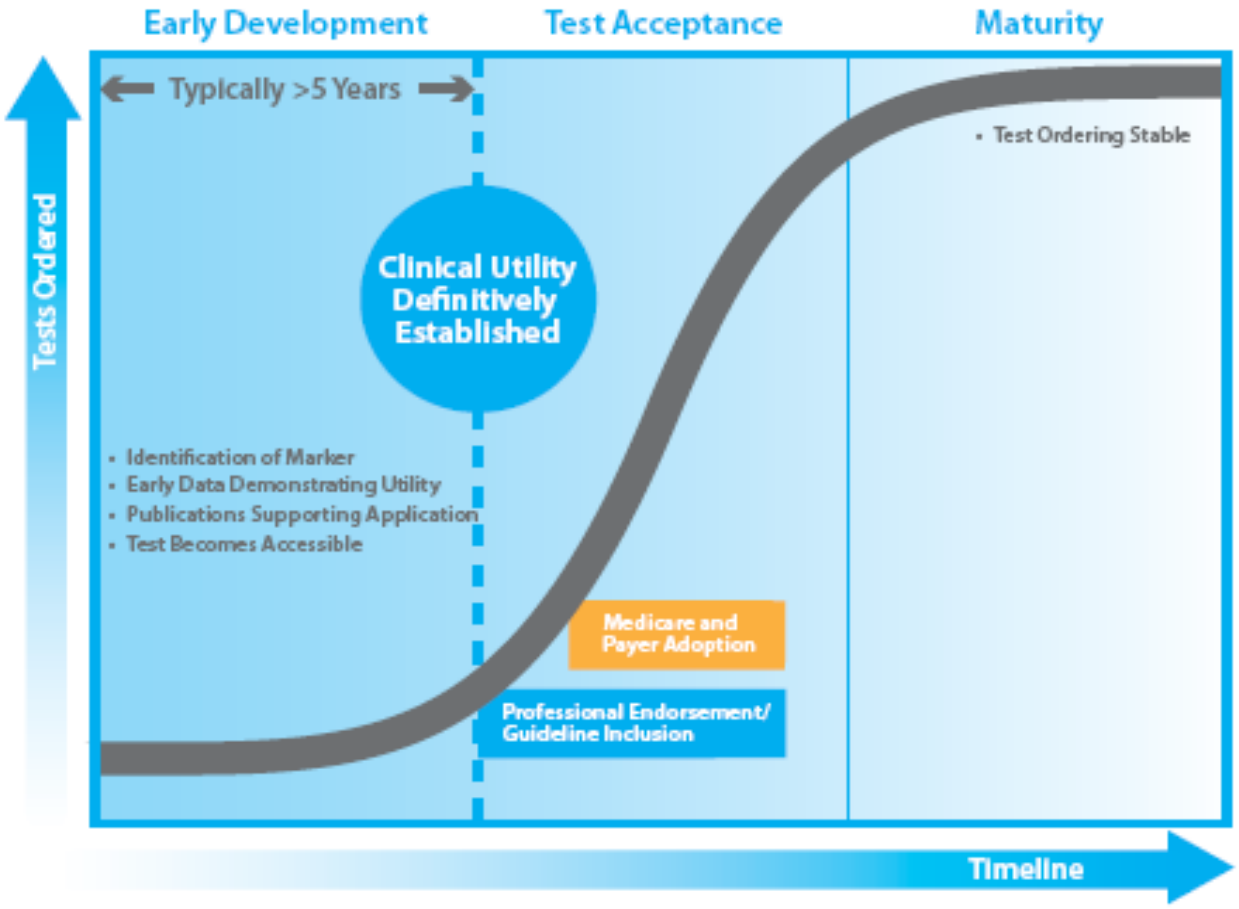
Rubin & Garroway, Nature 2011, 407:214.

Why is it taking so long?!

- Complex human diseases display a lot of genomic heterogeneity
  - Each disease phenotype has its own spectrum of underlying genetic polymorphisms
- *Clinical feasibility* is one of the bottlenecks
  - Need access to well qualified patient specimens for biomarker feasibility
- *Clinical validation* is a bigger bottleneck
  - Multiple, statistically powered clinical studies need to be conducted to demonstrate utility
- *Clinical utility* is the ultimate bottleneck
  - Need to demonstrate a medical economic benefit in order to achieve reimbursement

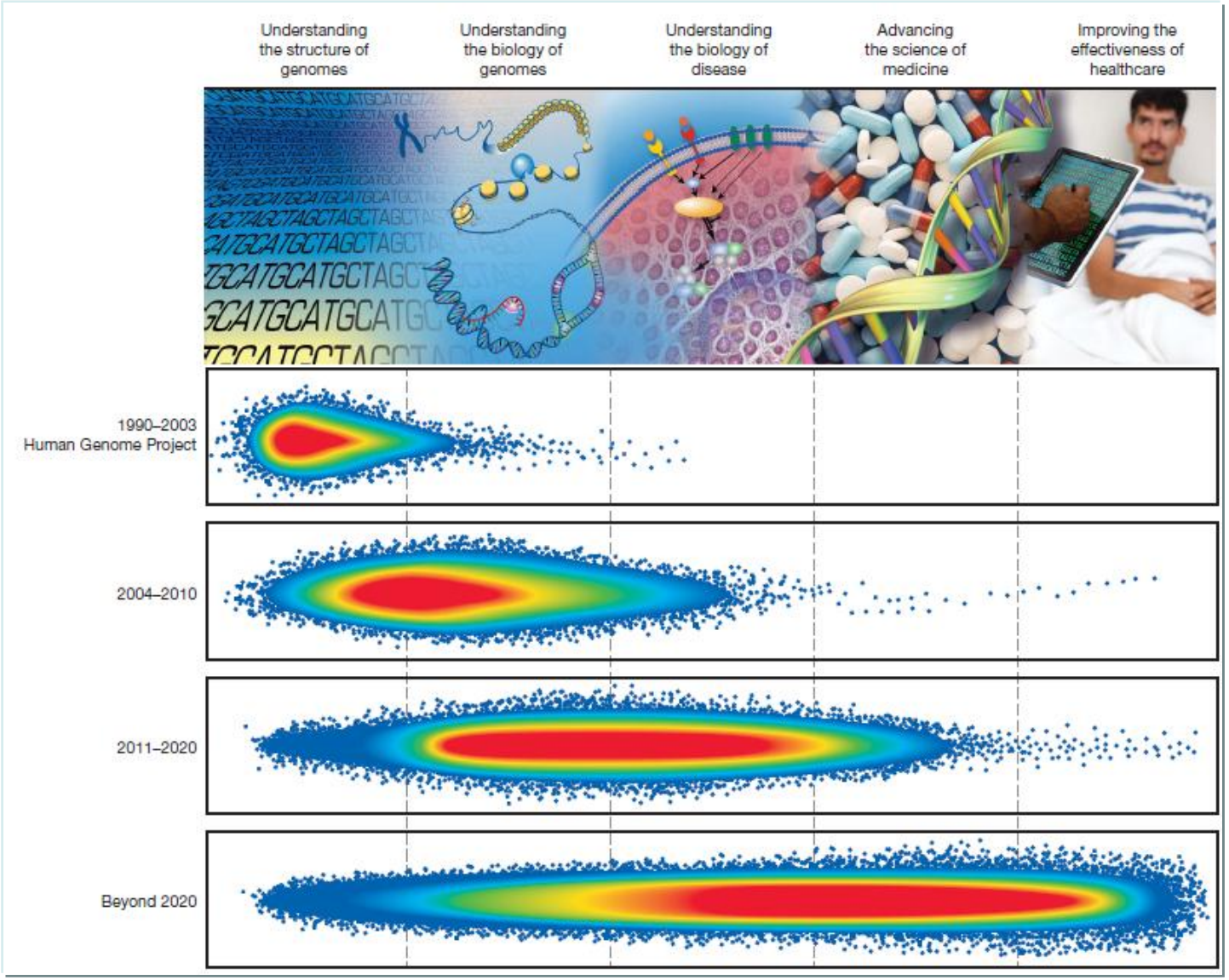
Companion Test Adoption Curve

How does the poor diagnostic company make any money?



Lai-Goldman & Faruki 2008. Genetics in Medicine 10: 874-78.

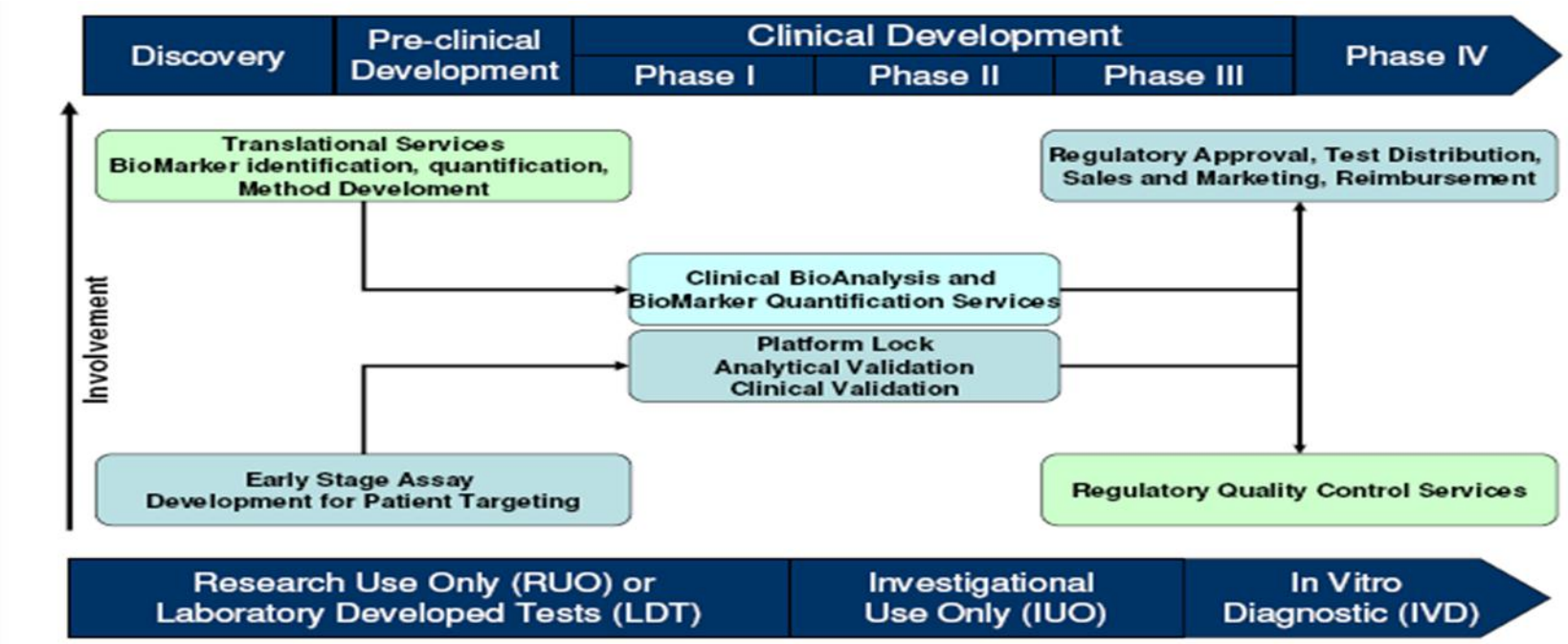
NHGRI's Roadmap – *circa 2011*



Eric Green, Nature 2011, 470:204

Pharmaceutical and Diagnostic Companies *must* Collaborate to Accelerate the Process

Parallel Development of Therapeutic and Companion Diagnostic



Sources: Adapted from "Drug-Diagnostic Co-Development Concept Paper" (FDA Publication, April 2005), and FW Freuh, "An Update on FDA Guidance's Related to Pharmacogenomics" (June 16, 2005).

Summary

- Companion Diagnostics represent an attractive growth opportunity for diagnostic companies
  - *A huge unmet need in a world of rising healthcare costs and diminishing returns with "one size fits all" drug development*
- We are seeing incremental advances, but the true promise of personalized medicine is still decades away
  - *A commitment to regulatory approval will be essential for long term growth*
- There are mutual incentives for pharmaceutical and diagnostic companies to collaborate
  - *Successful execution requires a clear understanding of clinical utility to balance and prioritize risk*