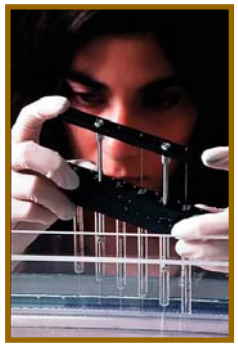

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High Impact Diagnostics

February 2014

Halteres from Ancient Greece
National Archaeological Museum in Athens

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What are some examples of high impact diagnostics?

- PSA
- Cholesterol
- HIV viral load
- HCV viral load
- Breast cancer prognosis (BRCA, Oncotype)
- Vitamin D testing
- HbA1c
- TB DNA
- Many others

How can we predict what is likely to be a high impact diagnostic?

- How can we identify new potential high impact diagnostics?
- How can we determine how well they need to perform?
- How can we actually plan to create a high impact diagnostic?

Many New Diagnostics Don't Make the Grade

- Many diagnostic tests are developed every year
- Few ever become "high impact" products
- Why? There are many reasons
- They just don't perform well enough
  - ✓ Sensitivity
  - ✓ Specificity
  - ✓ Reproducibility
- The clinical evidence base just isn't sufficient
  - ✓ Too few published clinical studies
  - ✓ Studies too small
- There is poor reimbursement
- Poor attempts to educate physicians

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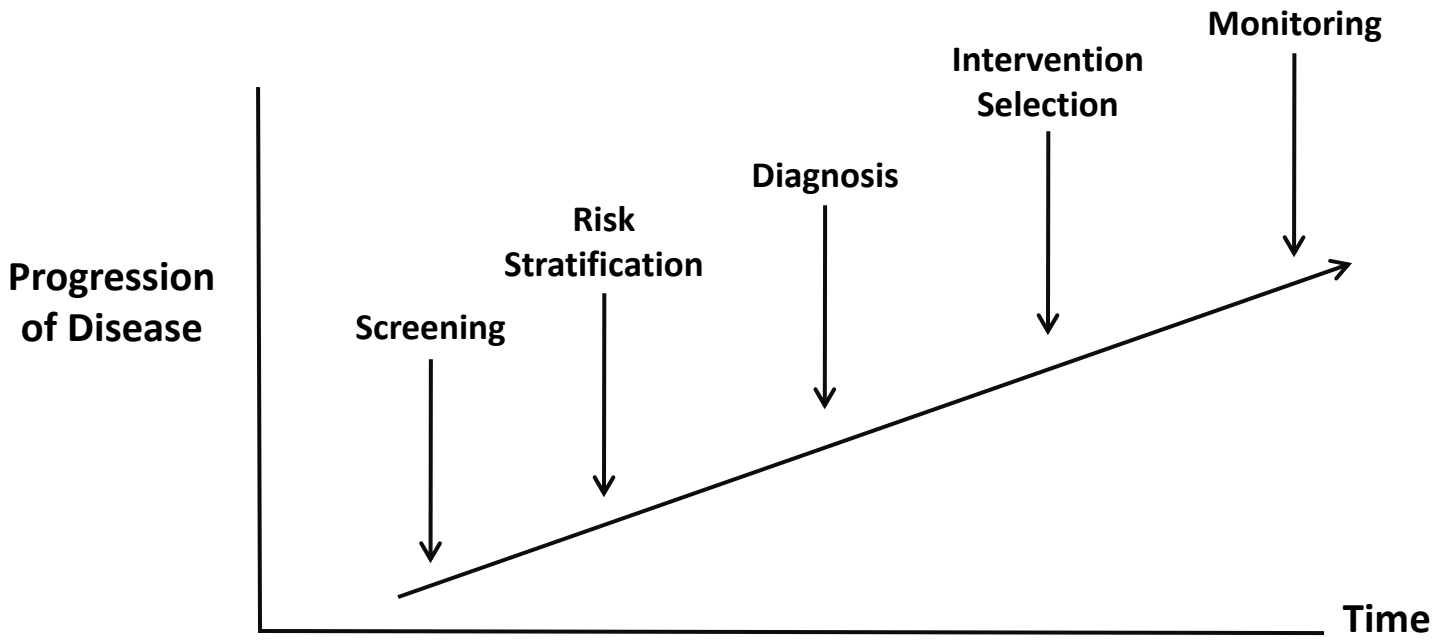
Diagnostics Tests Can Be Grouped Based Upon Progression of Disease

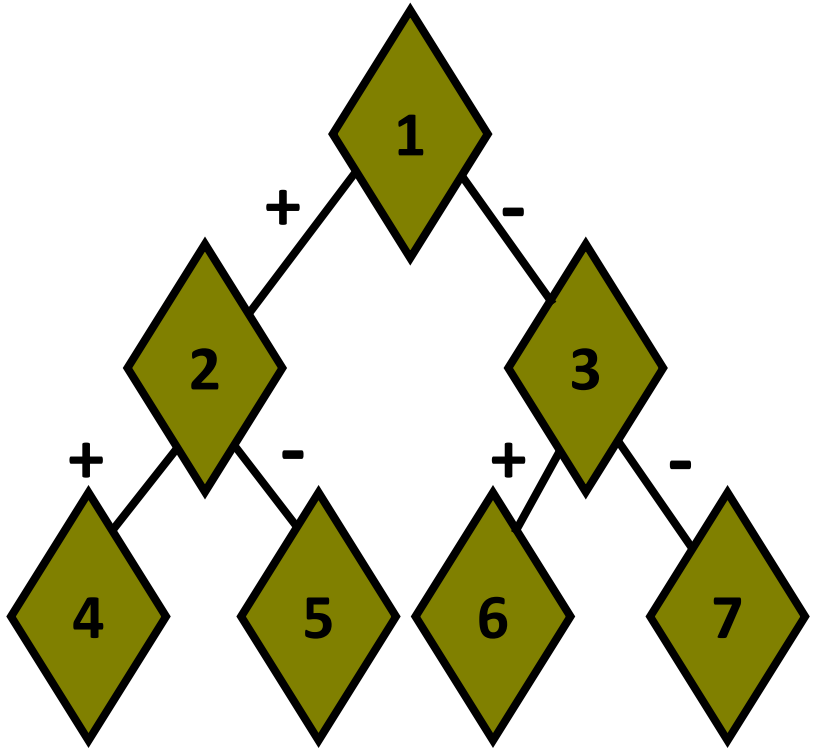
New diagnostics are needed in all categories



Searching for Diagnostics Opportunities: Disease Decision Trees

At each decision point:

- What is the quality of the decision today?
- What is the clinical impact of the decision?
- What is the economic impact of the decision?



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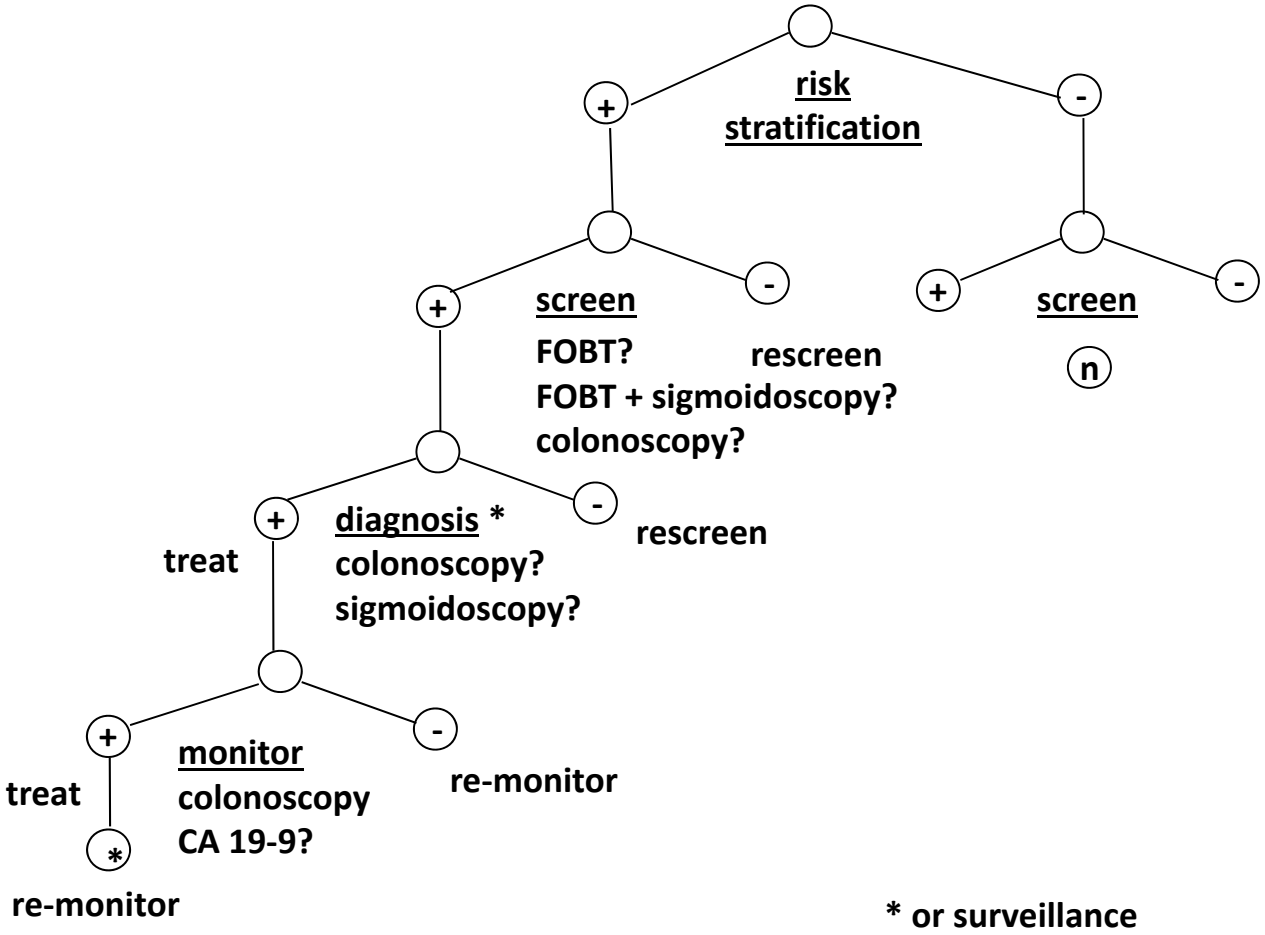
Colorectal Cancer Decision Tree Summary



Measure of a New Test Value: CER

Cost Effectiveness Ratio calculated by applying the formula below to two model estimates (one with and one without the new test)

$$\frac{\blacktriangle \$ \text{ Disease Cost}}{\blacktriangle \text{ Life Years Saved}}$$

Rule of Thumb for CERs (US Perspective)

- Ideal would be cost saving (save money)
- Second best would be cost effective
- CER of $20,000/LY ~ great value
- CER less than $50,000/LY ~ acceptable value for most US interventions
- CER between $50,000 and $100,000/LY is expensive
- CER greater than $100,000/LY is unacceptable

Example Cost Effectiveness Ratios (CERs)

Intervention	Cost/LY Saved
Angiography for MI	$21,831
Mammography	$25,000
Coronary Bypass	$40,000
HAART for HIV Disease	$15,000
Blood pressure medications	$5,000 - $72,000
Screen for Hemochromatosis	$9,900
NICU for babies <1000g	$5,100
Seatbelts in school buses	>$1,000,000

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Calculating the Performance Needed: Health Economic Modeling

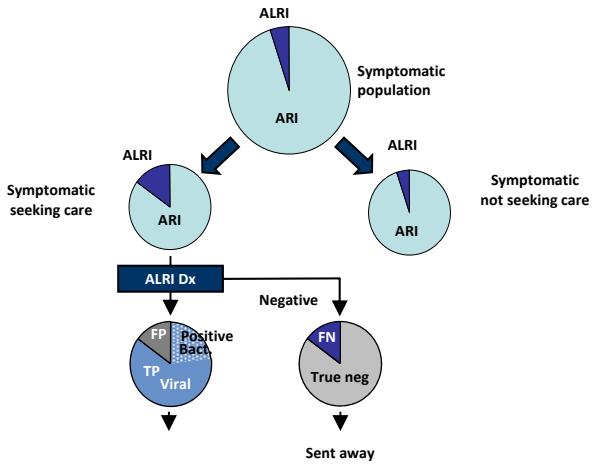
- Defined patient
- population

Diagnoses using existing methods

- True negatives
- False negatives
- True positives
- False positives

Diagnoses using new methods

- True negatives
- False negatives
- True positives
- False positives



- **Cost**
- **Mortality (life years lost)**

Compare to determine savings and life years gained

- **Cost**
- **Mortality (life years lost)**

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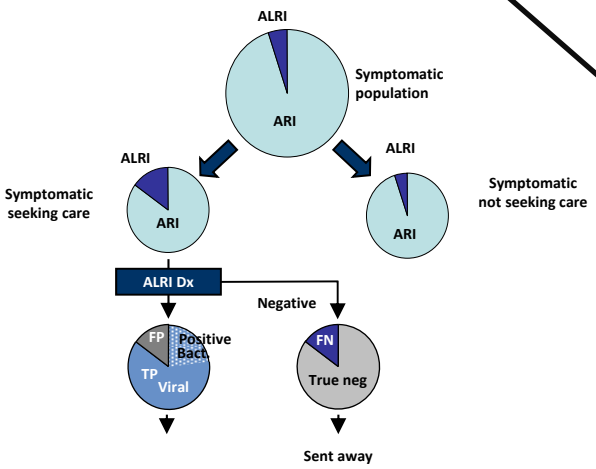
Calculating the Performance Needed: Health Economic Modeling

Clinical

Cost evaluation/patient = $0.35
Total cost evaluation = $970.00



True negatives	
% patients	65.5%
Number patients	1,800
Cost per patient	$0
Total cost	$0
Mortality rate	0%
Deaths	-

False negatives	
% patients	3.6%
False negatives	100
Cost per patient	$0
Total cost	$0
Mortality rate	30%
Deaths	30

True positives	
% patients	14.5%
Number patients	400
Cost per patient	$66
Total cost	$26,500
Mortality rate	10%
Deaths	40

False positives	
% patients	16%
Number patients	450
Cost per patient	$66
Total cost	$29,813
Mortality rate	0%
Deaths	-

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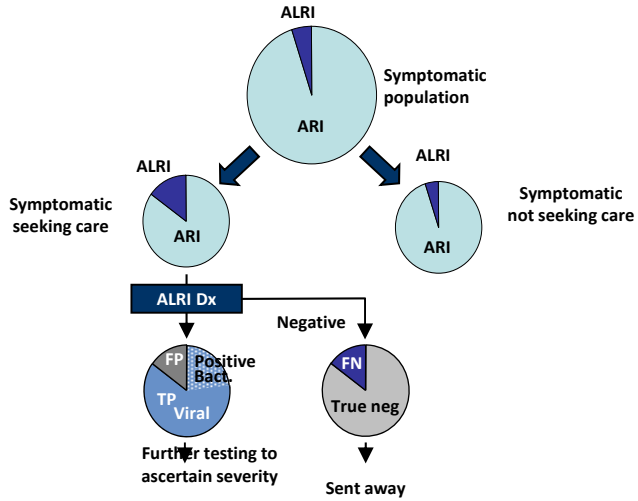
Calculating the Performance Needed: Health Economic Modeling

		ALRI test specificity					
		75%	80%	85%	90%	95%	100%
ALRI test sensitivity	75%	-$2.1	$0.6	$3.3	$6.0	$8.7	$11.4
	80%	-$2.7	$0.0	$2.7	$5.4	$8.1	$10.8
	85%	-$3.3	-$0.6	$2.1	$4.8	$7.5	$10.2
	90%	-$3.9	-$1.2	$1.5	$4.2	$6.9	$9.6
	95%	-$4.5	-$1.8	$0.9	$3.6	$6.3	$9.0
	100%	-$5.1	-$2.4	$0.3	$3.0	$5.7	$8.4

Per 1% improvement result in savings per patient diagnosed:

- **Sensitivity = $0.12**
- **Specificity = $0.54**



High Impact Diagnostics

- New tests will be successful if they:
  - ✓ Help to improve a decision in the decision tree
  - ✓ Are clinical meaningful
  - ✓ Are cost effective or cost saving

How do people develop new high impact diagnostics?

- We'll look at a fictitious company that wants to develop a new HIV viral load diagnostics product
- We'll follow the decision process for this company

Fictitious Example: RetroViraTech (RVT)

- RVT wants to develop an HIV viral load diagnostic testing device
- RVT is investigating prototype methods and devices
- RVT needs to determine its path to commercialization

Commercial Opportunity Attractiveness: RVT's Homework

- Size of potential market
- The clinical question to be answered using their test
- Performance requirements based upon economics
  - ✓ Cost of false positive? (for instance, treat healthy people) Implies specificity requirement (70%? 99%?)
  - ✓ Cost of false negative? (for instance, don't treat those who need it) Implies sensitivity requirements (70%? 99%?)
- Competition and IP (this can be a significant issue)
- Regulatory hurdles (FDA)
- Potential value (justifiable and affordable selling price)
- Time to meaningful sales (this can take longer than you think)

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Commercial Opportunity Attractiveness

Criteria	Weighting Factor	Score	Definition
Unmet Medical Need	**3**	**0**	Little impact on outcomes. Current diagnostic methods are sufficient. Difficult to change current medical practice
		1	Favorable impact on outcomes, although current methods exist. Iconix product would have a definable "value proposition"
		2	High unmet medical need. Major impact on quality of life. High cost disease.
Time to Meaningful Sales	**2**	**0**	>5 years after initial revenue
		1	2 - 5 years after initial revenue
		2	<2 years after initial revenue.
Economic Value	**3**	**0**	Niche market. Less than $500 million per year sales
		1	Market potential of $50 - $200 million per year sales.
		2	Market potential in excess of $200 million; investor "pizazz"
Market Size	**1**	**0**	<50,000 tests per year expected
		1	Population requiring testing is 50,000 to 200,000 tests per year
		2	Large population requiring >200,000 tests per year
Competition	**1**	**0**	Little differentiation; highly competitive
		1	Some competition but arguable that Iconix has a better solution
		2	Well suited for methodology. Less than or equal to two competitors
Special Interest Groups	**2**	**0**	Forgotten diseases; little evidence of special interest groups. Incoherent support.
		1	Some special interest groups but limited funding available
		2	Well supported by special interest groups
Partnership	**2**	**0**	Synergy with Rx or Dx unlikely
		1	Synergy with Rx or Dx likely but no Rx partner has yet been identified
		2	Clear synergy with Rx or Dx likely and potential partners exist

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Steps in the Creation of New Diagnostics Products

- Determine unmet medical need
- Determine user requirements
- Set product specifications
- Acquire or discover biomarkers
- Find or develop a testing platform that fulfills the user requirement
- Demonstrate the required performance
- Develop the commercial test or system
- Seek appropriate regulatory approvals
- Educate those who will benefit and those who will use it

User Requirements: What are they?

- An understanding of the needs and limitations of the customer including:
  - ✓ Sample and implications
  - ✓ System performance
  - ✓ System characteristics
  - ✓ Cost of ownership

Examples of User Requirements

- Sample type (collection issues, sample volume, storage temp, contamination issues, etc.)
- System performance (sensitivity, specificity, multiplex level, reproducibility, etc.)
- System characteristics (electricity, temperature control, user skill, quality control, waste issues, size, etc.)
- Cost of ownership (purchase, operating, maintenance, etc.)

Technical Likelihood of Success: What RVT Needs to Consider

- Do biomarkers already exist?
- If not:
  - ✓ What is the chance that there is a marker at high enough concentration to detect?
- Are there clinical samples available to prove the clinical utility?
- What are the clinical proof issues?
- Does a commercial testing system already exist that would work? (always faster)
- If not:
  - ✓ Is someone working on one that can be used in the near future?
  - ✓ How will a new system be developed?
- What are the product development hurdles?
- What is the timeline to product introduction?
- How difficult will it be to manufacture?
- From all of this, what are the product specifications?

Clinical Studies are Critical to Success

- The size of the sample bank is very important
  - ✓ Need 50 or more “events” for 1 marker
  - ✓ Need 100-250 “events” for 10 markers
  - ✓ “Normal” samples should be 2-3X the number of disease samples
- Clinical annotations are often poor
- Samples are often stored improperly
- Enough samples will be needed for research, development and regulatory approval (clinical validation)
- Need to have an untouched cohort for FDA approval
- Acquisition of samples is usually the toughest part of diagnostics research
- You must publish papers that support reimbursement

Technology Probability of Success

Criteria	Weighting Factor	Score	Definition
Availability of Samples	**3**	**0**	There are no sample banks yet identified and collecting samples will take > 9 months
		1	There are no sample banks yet identified or sample banks exist for discovery only and collecting samples will take < 9 months
		2	Banked samples exist for both discovery and validation and it is likely that we will be able to gain access to them without sacrificing too much
Time to Market	**3**	0	>5 years to initial revenue with high risk
		1	2 - 5 years required for initial revenue with moderate risk
		2	<2 years to initial revenue with a high probability of success
Technological Fit	**3**	**0**	Difficult sample type Other technological approach will likely prevail. Highly complex disease and difficult to collect/interpret data and samples.
		1	Specialized samples required for testing (tissue or CSF). Possible competitive approaches.
		2	Well suited for methodology. Measurement is on accessible sample type (plasma,
Regulatory Hurdles	**2**	**0**	Major regulatory hurdles; long, involved proof of principle and value support
		1	Some regulatory hurdles but achievable within two years of submission
		2	Few regulatory issues; existing diagnostics predicate of sufficient value
Intellectual Property	**1**	0	No or weak patent protection
		1	Patents submitted but not yet issued
		2	Strong patent portfolio; patents already issued; high likelihood of licensing revenue

Product Design Specification

- Developed by a Product Development Team from the User Requirements
  - ✓ Team should have representatives from research, development, manufacturing, engineering, software, quality, regulatory, marketing, and a team leader
- Specifications for all system components
  - ✓ Size, color, user interface, composition, materials, number of containers, shipping requirements, storage, labeling, rare reagents, detection system, stability needs, weight, volumes, vendors, software specifications, final costs, etc., etc.
- Trade off of time to market, cost and performance
- Product specification document signed off by entire team, then management
- Complete a budget and project plan

Phases of Product Development: Research

- Research goals:
  - ✓ Academic research goal: discover something new
  - ✓ Industrial product research goal: determine the feasibility of a new product concept
- At the end, no new inventions are needed
- Performance is almost good enough
- Risks are identified and acceptable
- Now it's time for development…

Phases of Product Development: Development

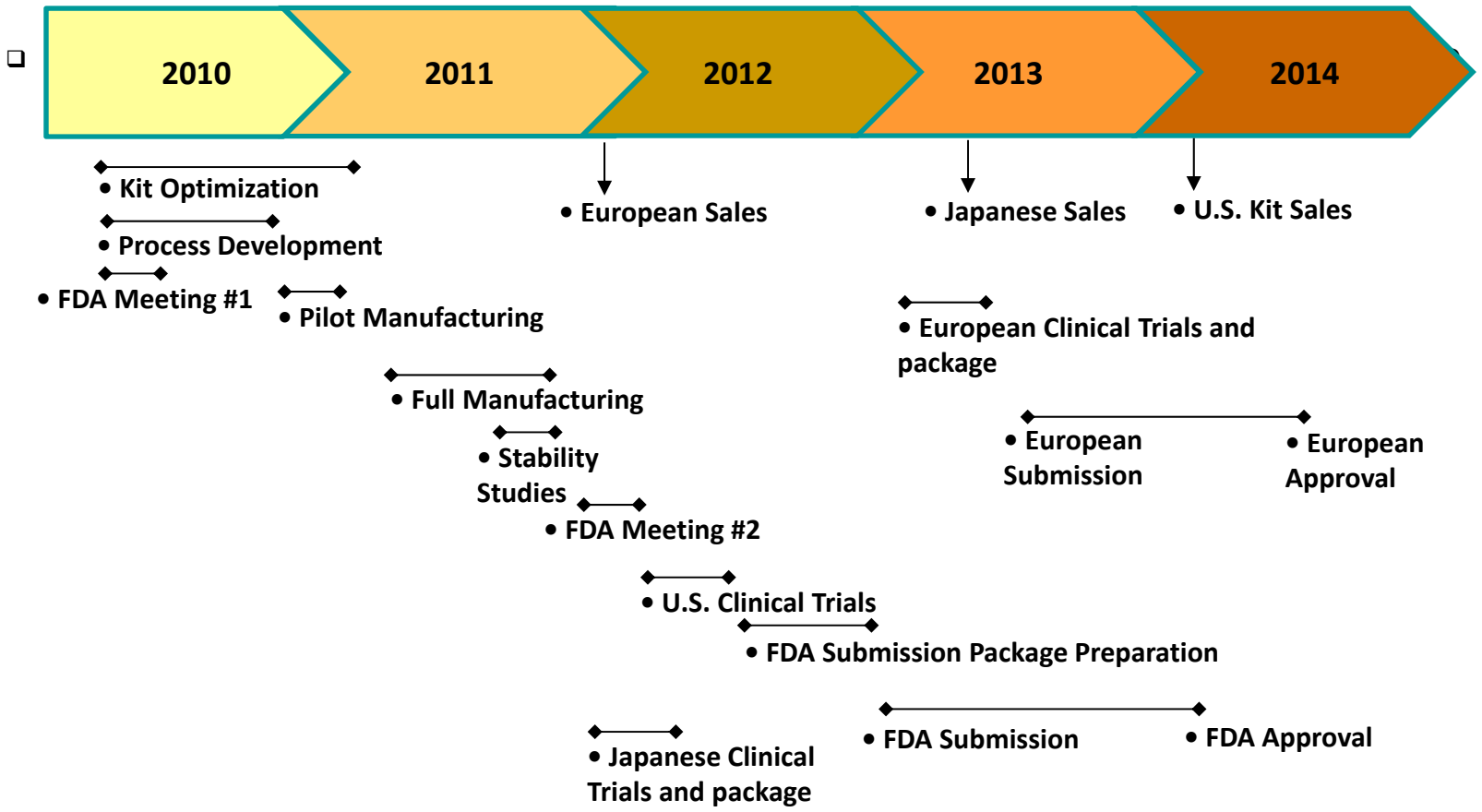
- Development involves:
  - ✓ Meeting product specifications
  - ✓ Optimization of performance
  - ✓ Optimization for manufacturing
  - ✓ Prepare for manufacturing…

} *Sometimes these two things are in conflict*

Phases of Product Development: Manufacturing

- Manufacturing involves:
  - ✓ Development of production methods
  - ✓ Production
  - ✓ Quality Control
  - ✓ Shipping
  - ✓ Storage
  - ✓ Supply chain

Global Diagnostic Company's Activities



OK, RVT Has a Plan

- Now comes the hard part…making it happen
  - ✓ Money
  - ✓ The right people
  - ✓ Execution of plan
  - ✓ Market the product

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Creation of New High Impact Diagnostics Products

- Understand the unmet need
- Determine user requirements
- Set product specifications
- Acquire or discover biomarkers
- Find or develop a testing platform
- Demonstrate the required performance
- Develop the commercial test or system
- Seek appropriate approvals
- Educate those who will use it

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What does a new diagnostic opportunity look like?

- Quality of decision is poor today (perhaps it is not made at all)
- Clinical impact is high
- Economic impact is high
- Commercial attractiveness is good
- Technical probability of success is high
- Regulatory path is clear
- Clear definition of customers
- Clear route to payment
- Acceptance is likely in a reasonable time frame
- Freedom to operate (IP)
- Development is affordable
- Organization has a competitive edge
- The investment makes sense

What are some examples of high impact diagnostics?

- PSA
- Cholesterol
- HIV viral load
- HCV viral load
- Breast cancer prognosis (BRCA, Oncotype Dx)
- Vitamin D testing
- HbA1c
- TB DNA
- Your test here

About Halteres Associates, LLC

www.halteresassociates.com

Halteres Associates is a leading bioscience consultancy comprised of more than150 professionals with extensive, long-term, direct operating experience in a broad spectrum of areas of expertise, including the development and commercialization of diagnostics, medical devices, therapeutics, research reagents and bioscience tools. Halteres team members have been personally involved, at direct operating and senior management levels, in the planning and growth phases of several of the industry's most successful diagnostics ventures, including Abbott, ABI, Bayer, Chiron, Ciba Corning, Life Technologies, Ortho, Roche, Siemens, and others. Areas of core competency include strategic planning, business development, product and market development, portfolio planning, business and financial modeling, impact analyses, including health economics and reimbursement, clinical study design and management, regulatory strategy, sales and marketing, clinical laboratory management, global health and much more. Halteres leverages these individual skills by assembling customized consulting teams that best meet the unique needs of our clients. The interactions of these experienced team members and the resulting syntheses of ideas and actions provide our clients with the greatest value and set us apart from other consulting firms. To date, Halteres Associates has assisted clients in achieving more >$1B in cumulative M&A and funding transactions.

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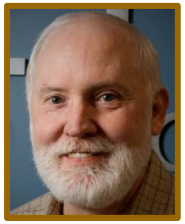

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