What does the Future Hold for Molecular Diagnostics Reimbursement Policy?

Washington March 19 9 am

Bruce Quinn MD PhD

Foley Hoag LLP

bquinn@foleyhoag.com

FOLEY HOAG LLP

Driving Business Advantage

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American Clinical Laboratory Association


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Clinical lab tests guide more than 70% of medical decisions. Lab tests save time, money, and lives by enabling early detection and prevention of disease.


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Challenges & Opportunities Facing Laboratories in the 21st Century
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THE DARK REPORT

Payors and Vision

Lack of Foresight

Diagnostics Value is Hard

Next Steps

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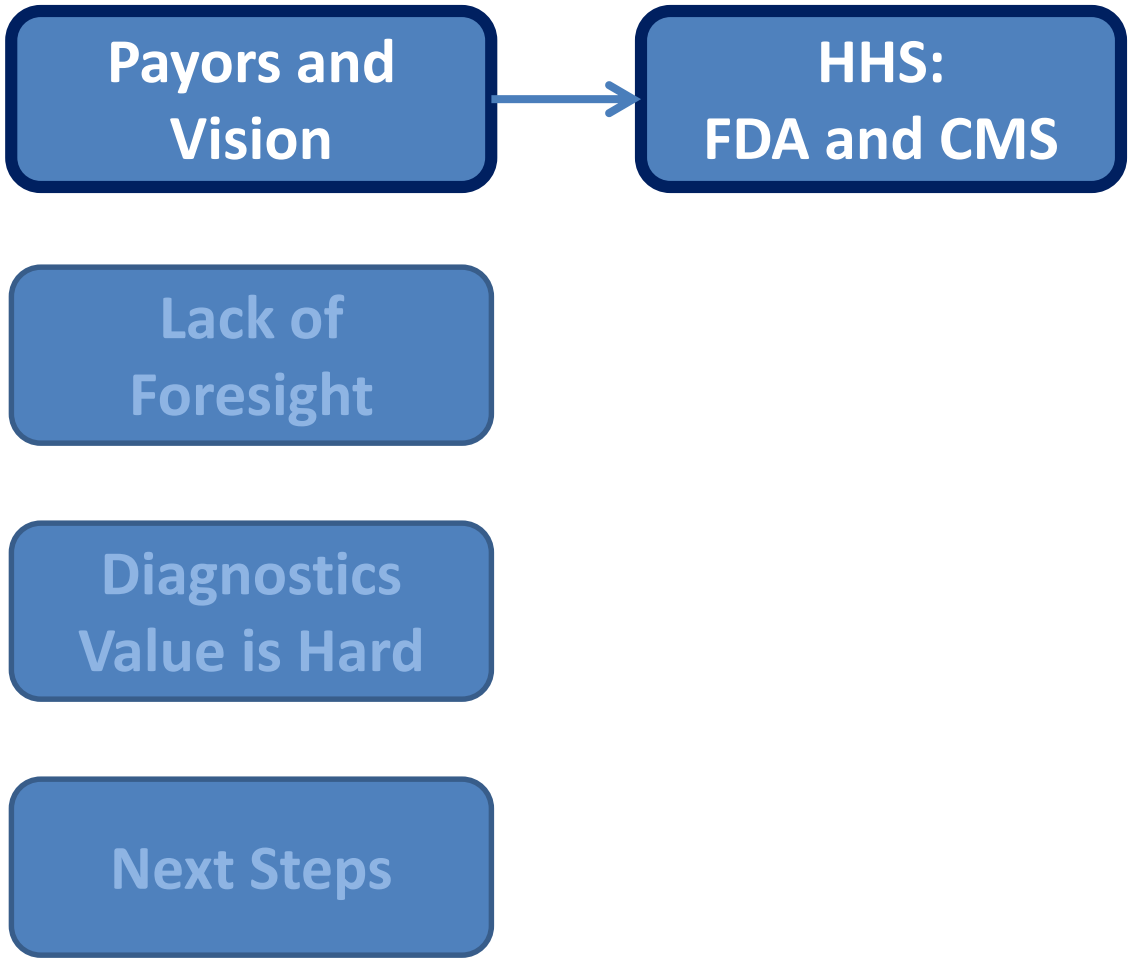

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- **Personalized Medicine:**

  FDA issues 60-page cross agency report on efforts to improve and advance Personalized Medicine

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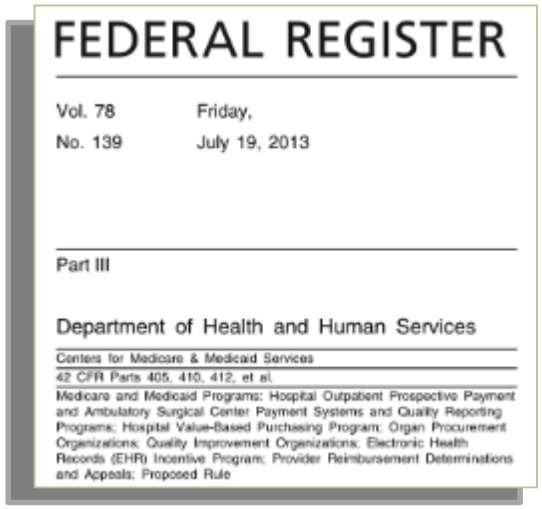
  CMS proposes 5 new policies to cut pricing for personalized medicine diagnostics



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FDA: The Talker

Bloomberg

FDA Tells Google-Backed 23andMe to Halt DNA Test Service

By Anna Edney - Nov 25, 2013 5:33 PM ET

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FDA: The Talker

Bloomberg

FDA Tells Google-Backed 23andMe to Halt DNA Test Service

By Anna Edney - Nov 25, 2013 5:33 PM ET

Nov 22, 2013

Ann Wojcicki
CEO
23andMe, Inc.
1390 Shoreline Way
Mountain View, CA 94043

Document Number: GEN1300666
Re: Personal Genome Service (PGS)

WARNING LETTER

Dear Ms. Wojcicki,

The Food and Drug Administration (FDA) is sending you this letter because you are marketing the 23andMe Saliva Collection Kit and Personal Genome Service (PGS) without marketing clearance or approval in violation of the Federal Food, Drug and Cosmetic Act (the FD&C Act).

This product is a device within the meaning of section 201(h) of the FD&C Act, 21 U.S.C. 321(h), because it is intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or is intended to affect the structure or function of the body. For example, your

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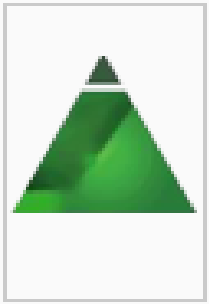
Analyst Blog »



MYGN Battles Odds, Shares Fall

by Zacks Equity Research Published on December 04, 2013 | No Comments

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Analyst Blog »

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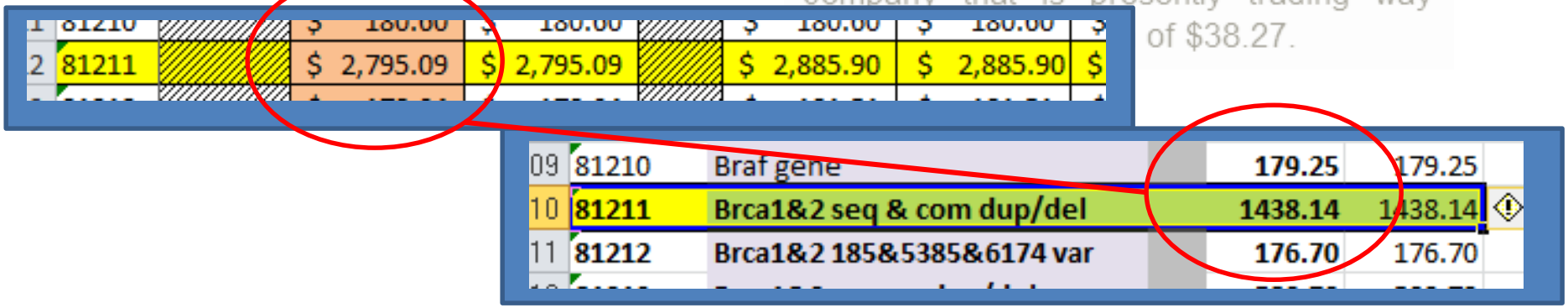
ALIOF AMAG MYGN HSKA

Shares of **Myriad Genetics Inc.** (MYGN - Analyst Report) registered a steep decline of 9.3%, closing the session at $26.98 on Dec 2, 2013. The downfall continued the following day with a fall of 5.3% and closed at $25.55. The two heavy setbacks pulled down the stock price of the company that is presently trading way of $38.27.



2	81211		$ 2,795.09	$ 2,795.09		$ 2,885.90	$ 2,885.90	$

09	81210	Braf gene	179.25	179.25
10	81211	Brca1&2 seq & com dup/del	1438.14	1438.14
11	81212	Brca1&2 185&5385&6174 var	176.70	176.70

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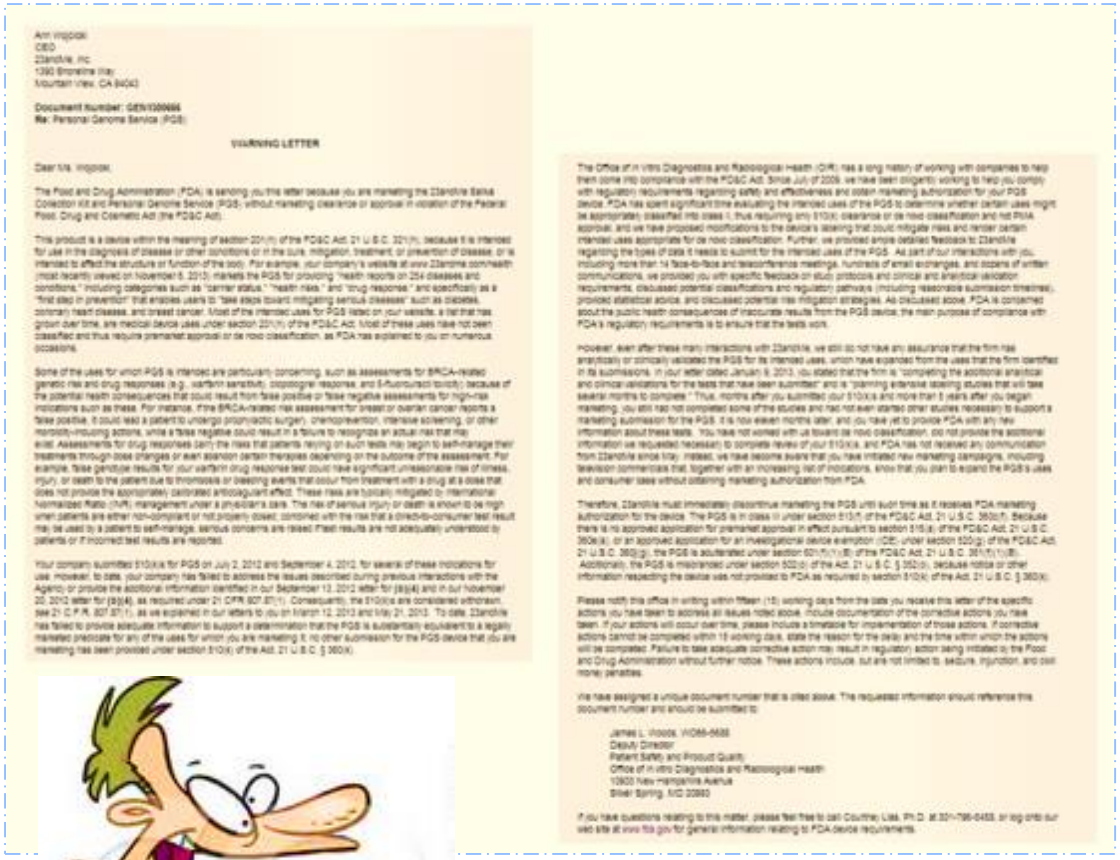
FDA



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Some of the uses for which PGS is intended are particularly concerning, such as assessments for BRCA-related genetic risk and drug responses (e.g., warfarin sensitivity, clopidogrel response, and 5-fluorouracil toxicity) because of the potential health consequences that could result from false positive or false negative assessments for high-risk indications such as these. For instance, if the BRCA-related risk assessment for breast or ovarian cancer reports a false positive, it could lead a patient to undergo prophylactic surgery, chemoprevention, intensive screening, or other morbidity-inducing actions, while a false negative could result in a failure to recognize an actual risk that may exist. Assessments for drug responses carry the risks that patients relying on such tests may begin to self-manage their treatments through dose changes or even abandon certain therapies depending on the outcome of the assessment. For example, false genotype results for your warfarin drug response test could have significant unreasonable risk of illness, injury, or death to the patient due to thrombosis or bleeding events that occur from treatment with a drug at a dose that does not provide the appropriately calibrated anticoagulant effect. These risks are typically mitigated by international normalized Ratio (INR) management under a physician's care. The risk of serious injury or death is known to be high when patients are either non-compliant or not properly dosed, combined with the risk that a directly-to-consumer test result may be used by a patient to self-manage, serious concerns are raised if test results are not adequately understood by patients or if incorrect test results are reported.

Your company submitted 510(k)s for PGS on July 2, 2012 and September 4, 2012, for several of these indications for use. However, to date, your company has failed to address the issues described during previous interactions with the Agency or provide the additional information identified in our September 13, 2012 letter for (b)(4) and in our November 20, 2012 letter for (b)(4), as required under 21 CFR 807.87(1). Consequently, the 510(k)s are considered withdrawn, see 21 C.F.R. 807.87(1), as we explained in our letters to you on March 12, 2013 and May 21, 2013. To date, 23andMe has failed to provide adequate information to support a determination that the PGS is substantially equivalent to a legally marketed predicate for any of the uses for which you are marketing it; no other submission for the PGS device that you are marketing has been provided under section 510(k) of the Act, 21 U.S.C. § 360(k).

The Office of In Vitro Diagnostics and Radiological Health (OIR) has a long history of working with companies to help them come into compliance with the FD&C Act. Since July of 2009, we have been diligently working to help you comply with regulation requirements regarding safety and effectiveness and obtain marketing authorization for your PGS device. FDA has spent significant time evaluating the intended uses of the PGS to determine whether certain uses might be appropriately classified into class II, thus requiring only 510(k) clearance or de novo classification and not PMA approval, and we have proposed modifications to the device's labeling that could mitigate risks and render certain intended uses appropriate for de novo classification. Further, we provided ample detailed feedback to 23andMe regarding the types of data it needs to submit for the intended uses of the PGS. As part of our interactions with you, including more than 14 face-to-face and teleconference meetings, hundreds of email exchanges, and dozens of written communications, we provided you with specific feedback on study protocols and clinical and analytical validation requirements, discussed potential classifications and regulation pathways (including reasonable submission timelines), provided statistical advice, and discussed potential risk mitigation strategies. As discussed above, FDA is concerned about the public health consequences of inaccurate results from the PGS device, the main purpose of compliance with FDA's regulatory requirements is to ensure that the tests work.

However, even after these many interactions with 23andMe, we still do not have any assurance that the firm has analytically or clinically validated the PGS for its intended uses, which have expanded from the uses that the firm identified in its submissions. In your letter dated January 9, 2013, you stated that the firm is "completing the additional analytical and clinical validations for the tests that have been submitted" and is "planning extensive labeling studies that will take several months to complete." Thus, months after you submitted your 510(k)s and more than 8 years after you began marketing, you still have not completed some of the studies and have not even started other studies necessary to support a marketing submission for the PGS. It is now eleven months later, and you have yet to provide FDA with any new information about these tests. You have not worked with us toward de novo classification, did not provide the additional information we requested necessary to complete review of your 510(k)s, and FDA has not received any communication from 23andMe since May. Instead, we have become aware that you have initiated new marketing campaigns, including television commercials that, together with an increasing list of indications, show that you plan to expand the PGS's uses and consumer sales without obtaining marketing authorization from FDA.

Therefore, 23andMe must immediately discontinue marketing the PGS until such time as it receives FDA marketing authorization for the device. The PGS is in class III under section 513(f) of the FD&C Act, 21 U.S.C. 360c(f). Because there is no approved application for premarket approval in effect pursuant to section 515(a) of the FD&C Act, 21 U.S.C. 360e(a), or an approved application for an investigational device exemption (IDE) under section 520(g) of the FD&C Act, 21 U.S.C. 360j(g), the PGS is adulterated under section 501(f)(1)(B) of the FD&C Act, 21 U.S.C. 351(f)(1)(B). Additionally, the PGS is misbranded under section 502(o) of the Act, 21 U.S.C. § 352(o), because notice or other information respecting the device was not provided to FDA as required by section 510(k) of the Act, 21 U.S.C. § 360(k).

Please notify this office in writing within fifteen (15) working days from the date you receive this letter of the specific actions you have taken to address all issues noted above. Include documentation of the corrective actions you have taken. If your actions will occur over time, please include a timetable for implementation of those actions. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which the actions will be completed. Failure to take adequate corrective action may result in regulatory action being initiated by the Food and Drug Administration without further notice. These actions include, but are not limited to, seizure, injunction, and civil money penalties.

We have assigned a unique document number that is cited above. The requested information should reference this document number and should be submitted to:

James L. Woods, WO66-5668
Deputy Director
Patient Safety and Product Quality
Office of In Vitro Diagnostics and Radiological Health
10903 New Hampshire Avenue
Silver Spring, MD 20993

If you have questions relating to this matter, please feel free to call Courtney Lias, Ph.D. at 301-796-5453, or log onto our web site at www.fda.gov for general information relating to FDA device requirements.

CMS

$2,795	
	$1,438

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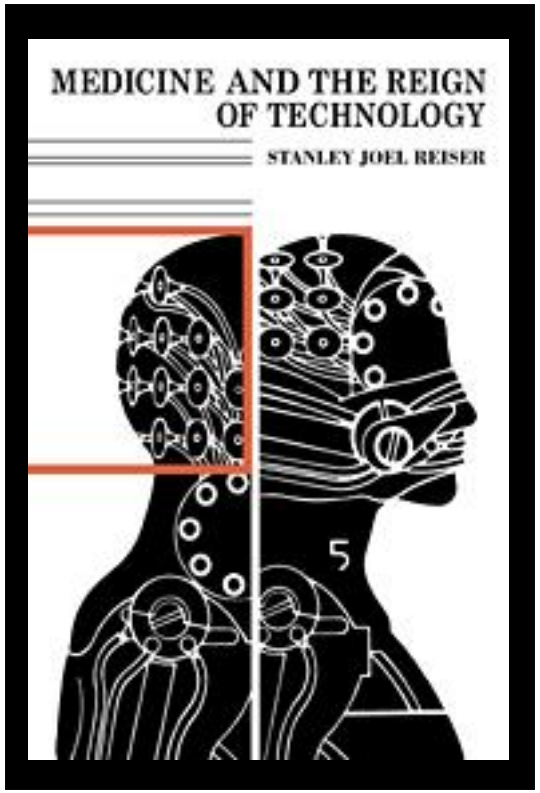
There is a century-old bias that diagnostic tests are over-used.

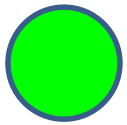


1978

A Parisian physician touring American hospitals in ***1912*** reported his surprise at the number of laboratory tests routinely requested…they seemed, "Like the Lord's rain, to descend from heaven on the just and the unjust in the most impartial fashion…"

In the ***1940s***, Harrison noted "the present day tendency towards a five-minute history followed by a five-day barrage of special tests in the hope that the diagnostic rabbit may emerge from the laboratory hat."

Studies in the ***1970s*** found that many laboratory tests ordered by doctors yielded little information that was new or useful.



The NEW ENGLAND JOURNAL of MEDICINE

The Path to Personalized Medicine

Margaret A. Hamburg, M.D., and Francis S. Collins, M.D., Ph.D.

SHATTUCK LECTURE

Innovation, Regulation, and the FDA

Margaret A. Hamburg, M.D.

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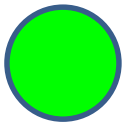

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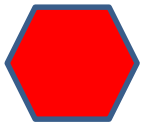

DEPARTMENT OF HEALTH AND HUMAN SERVICES

OFFICE OF INSPECTOR GENERAL

Memorandum Report: *Coverage and Payment for Genetic Laboratory Tests*, OEI-07-11-00011

COMPARING LAB TEST PAYMENT RATES: MEDICARE COULD ACHIEVE SUBSTANTIAL SAVINGS

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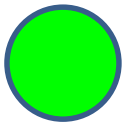

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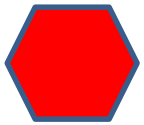

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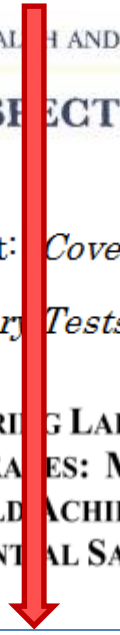

Fiscal Year 2015
Budget in Brief
Strengthening Health and Opportunity for All Americans

FDA

NIH

Fiscal Year 2015
Budget in Brief
Strengthening Health and Opportunity for All Americans

CMS

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Example

- Prostate cancer is #2 killer among cancers in men
- #1 killer among men who don't smoke

- Yet: Great concern about overdiagnosis, overtreatment

- PSA test is decades old = $23
- CMS gave clear examples it would price any new PSA-like test at $23

- **CMS seems willing to spend BILLIONS on unnecessary surgeries and biopsies**

✓ **Stakeholders working together should be able to do better**

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Payors and Vision ✓

Lack of Foresight

Diagnostics Value is Hard

Next Steps

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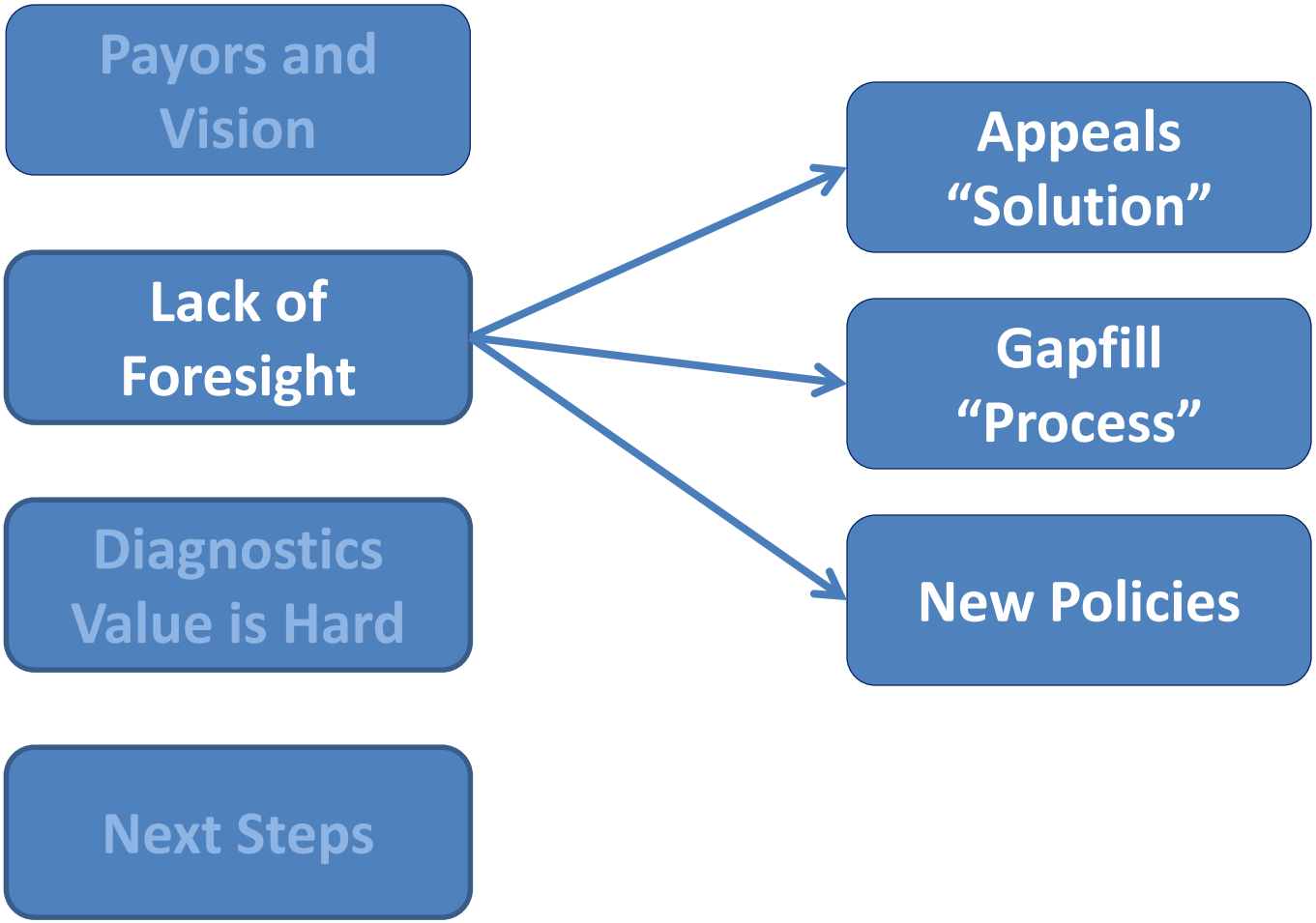

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HHS Delays ALJ Hearing Scheduling by Two Years: *Continues to Fail to Adhere to Its Own Regulations*

By Peter W. Thomas, JD, and Christina Hughes, JD, MPH

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	2012	2013	2014	2015
Claims	313,000	600,000	700,000	850,000
Staff	466	492	514	629
Money	72,000,000	69,000,000	82,000,000	100,000,000
Claims/Staff	672	1220	1362	1351
Cost/Claim	$ 230	$ 115	$ 117	$ 118

Current Backlog: 460,000 cases
Growth 2012-2013 (two years): From 92,000 to 460,000
Fell behind 370,000 cases while adjucating 600,000 cases
OMHA throughput is about 300-350,000 per year
Will take at about one year to clear current backload while 700,000 new cases arrive.
✓**During CY2015: 1,500,000 cases to be in backlog or arriving**

** Ahh…But… staff will increase 15%; and a filing e-system will be implemented...umm…*

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Money	72,000,000	69,000,000	82,000,000	100,000,000
Claims/Staff	672	1220	1362	2385
Cost/Claim	$ 230	$ 115	$ 117	$ 67

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"We majored in poli sci and went to law school, we didn't major in math."

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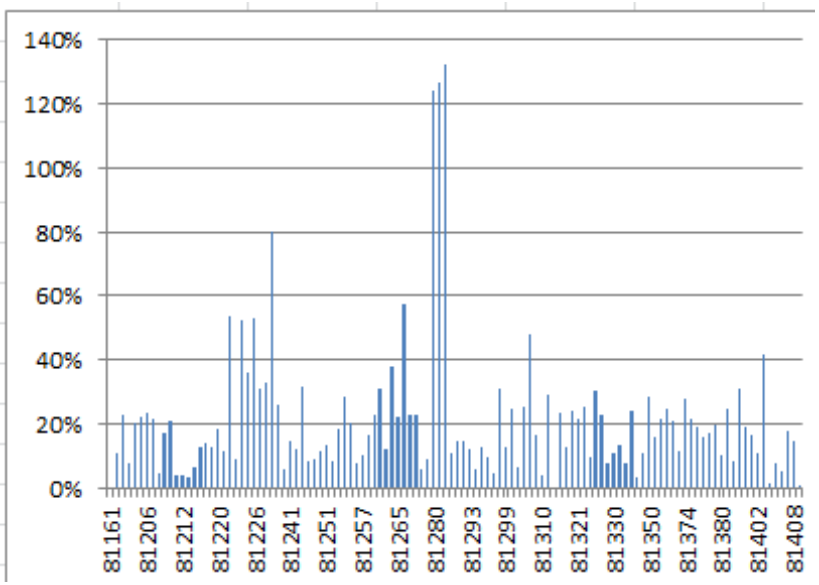
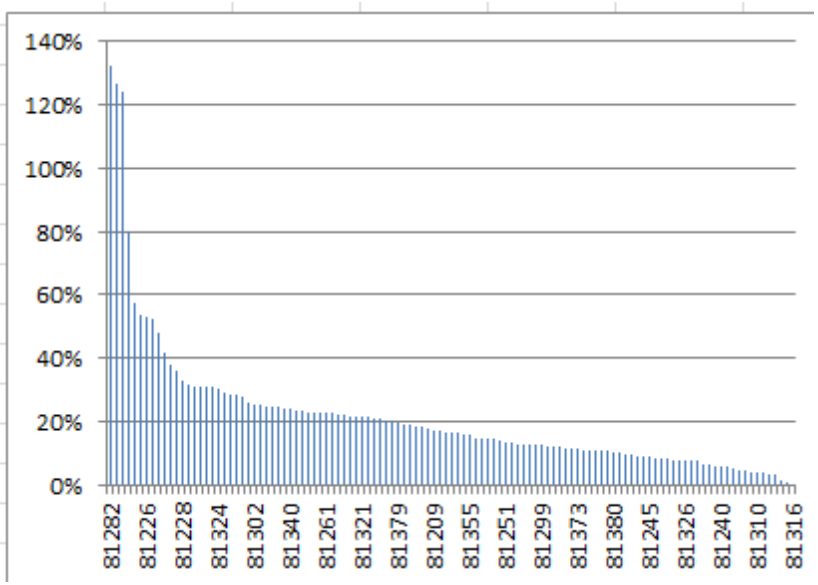
Standard Deviation of Proposed MAC Prices for MoPath tests





Standard Deviation of Proposed Prices as Percent of Average Price (May 2013)

* Some tests had almost no Std. Dev., others had 100% Std. Dev.

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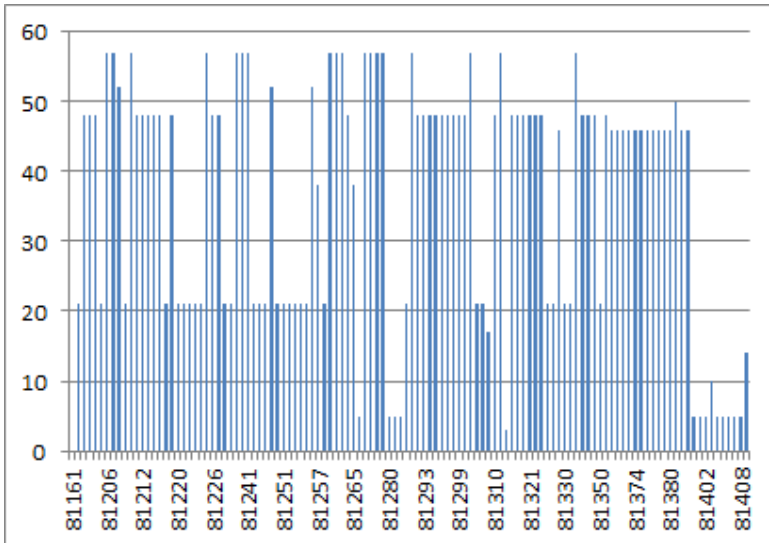
How Many MACs priced the test?



How Many MAC Prices The Code (By Code #)

(Note: Codes are sequential, but also alphabetical by gene name)

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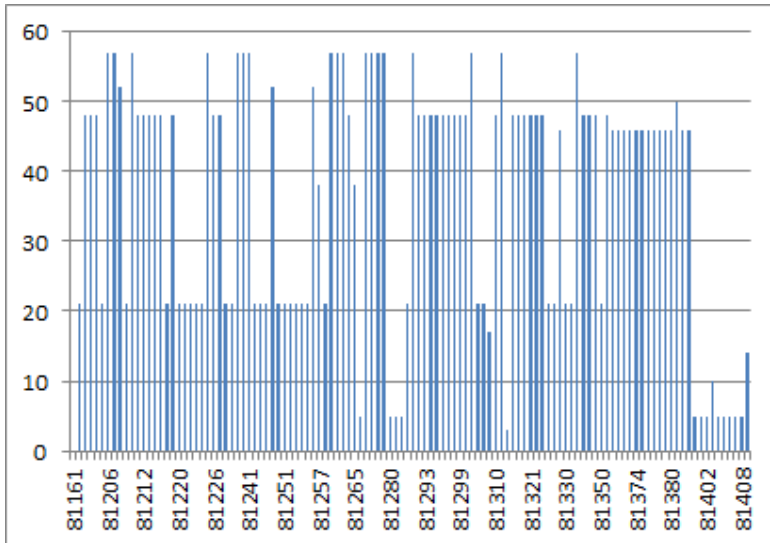
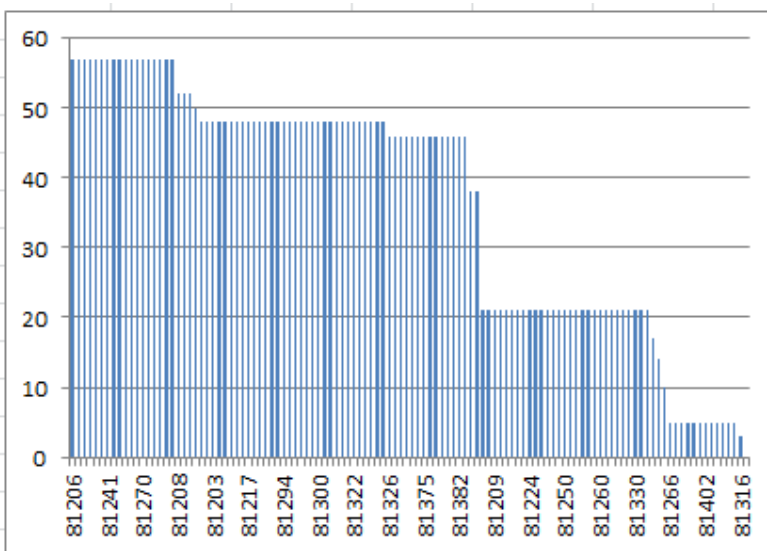
How many MACs priced the test?



How Many MAC Prices (By Code #)



Sorted By Density of Reporting MACs

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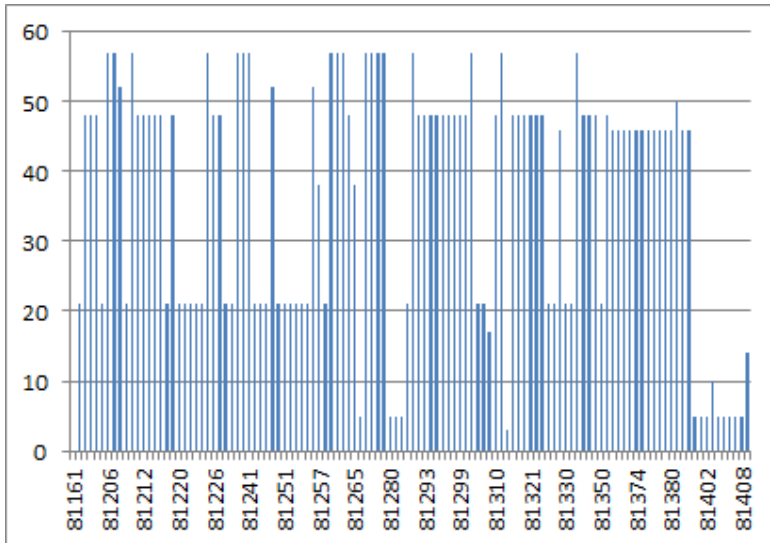
There seemed to be four categories:



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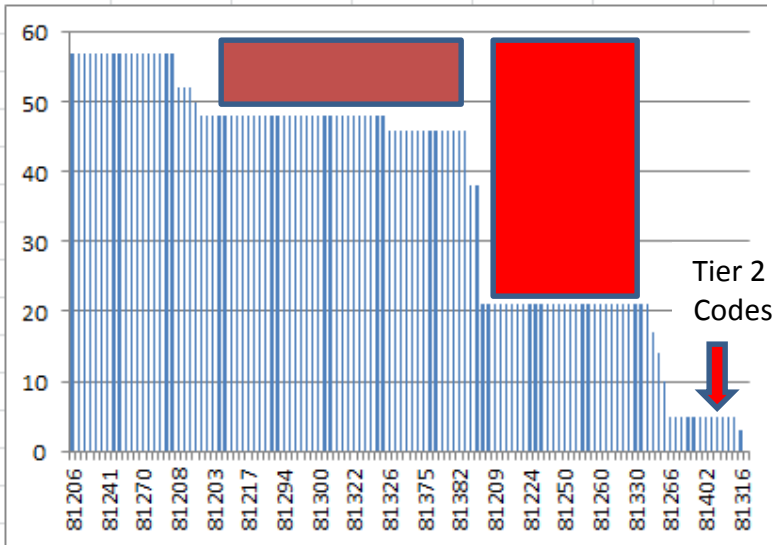

Sorted By Density of Reporting MACs

1 2 3 4

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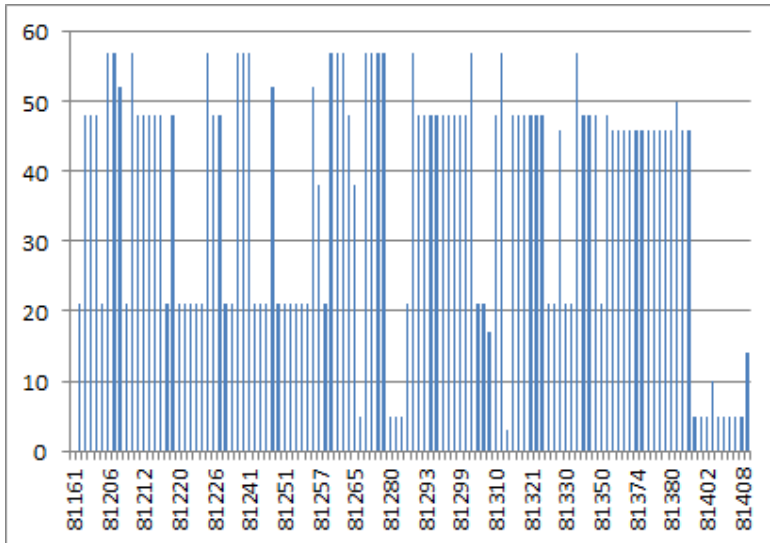
Lessons Learned?



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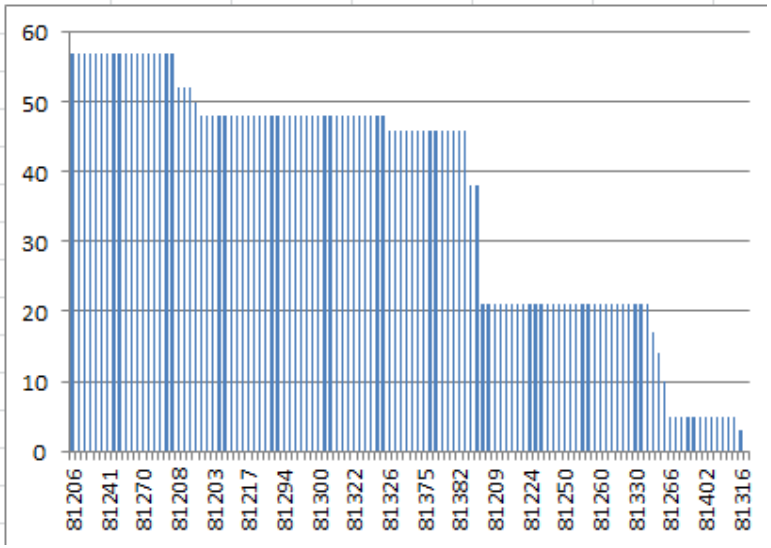

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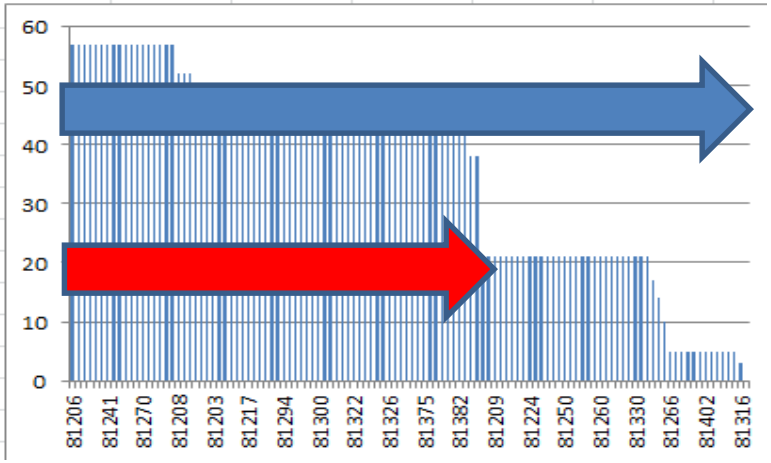

115 Codes in Gapfill Proposals (May)

72 Codes in September Medians

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Activity	2013 Concern	Outcome	2014 Outlook
Gapfill for genetic test pricing	**- Payments were dropping below costs, especially for validated FDA kits for combination diagnostics**	• Coalitions, Hill letters • Some changes	• Very poor policy environment for tests that require R&D and I.P. • Price to cost + 30%
Reprice the CLFS	**- CMS gave thin guidance as to methodology** **- "Technology" costs are only part of the price**	• CMS will move forward year by year • CMS could not display "an example"	• Process problems and concerns raised by stakeholders will still have to be faced
Bundle CLFS Tests and Pathology Tests (e.g. to hospital outpatient office visits)	**- Does control overutilization** **- But penalizes appropriate utilization too** **- Hard to enforce (patient crosses street)**	• CMS will move forward for CLFS • CMS declined to move forward for Pathology tests and Imaging tests	• Likely will soon face the "patient goes across the street" problem for lab tests
Cap Pathology Tests at "OPPS-APC" prices	**Didn't make sense based on arithmetic (each APC contains wide range of prices, pays the average, half are above average)**	• CMS will **not** do this for 2014…	• SGR S.2000 lets CMS price PFS/RVUs with a free hand • CCI edits acted as price cuts

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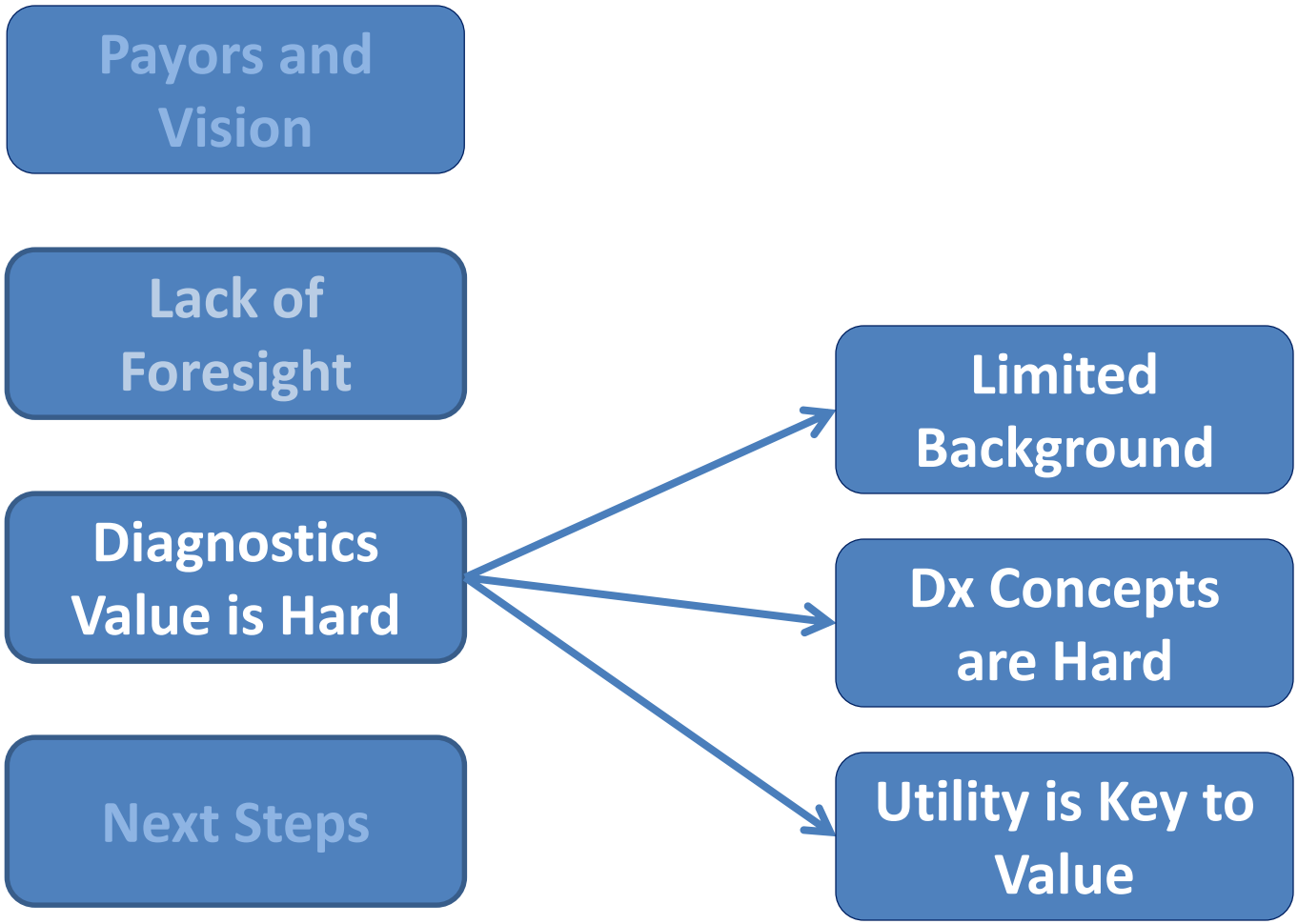

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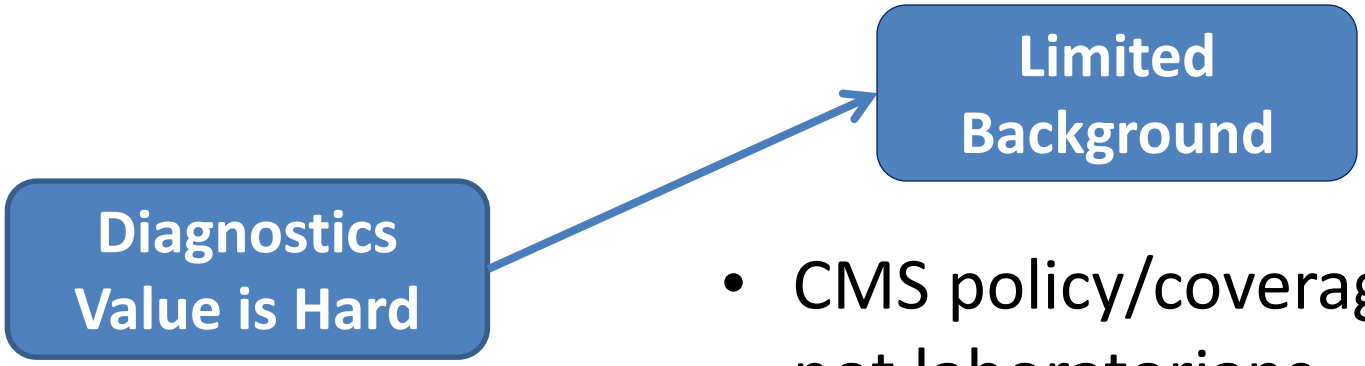

- CMS policy/coverage staff are not laboratorians
- Very, very few pathologists
- Physicians and pathologists may have trained 20-40 years ago
- Non clinicians do not have industry based perspective

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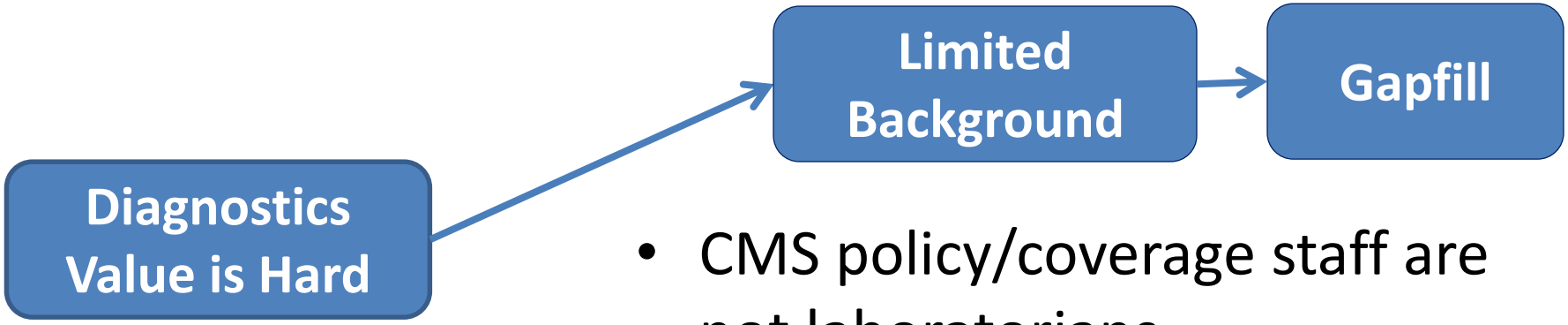

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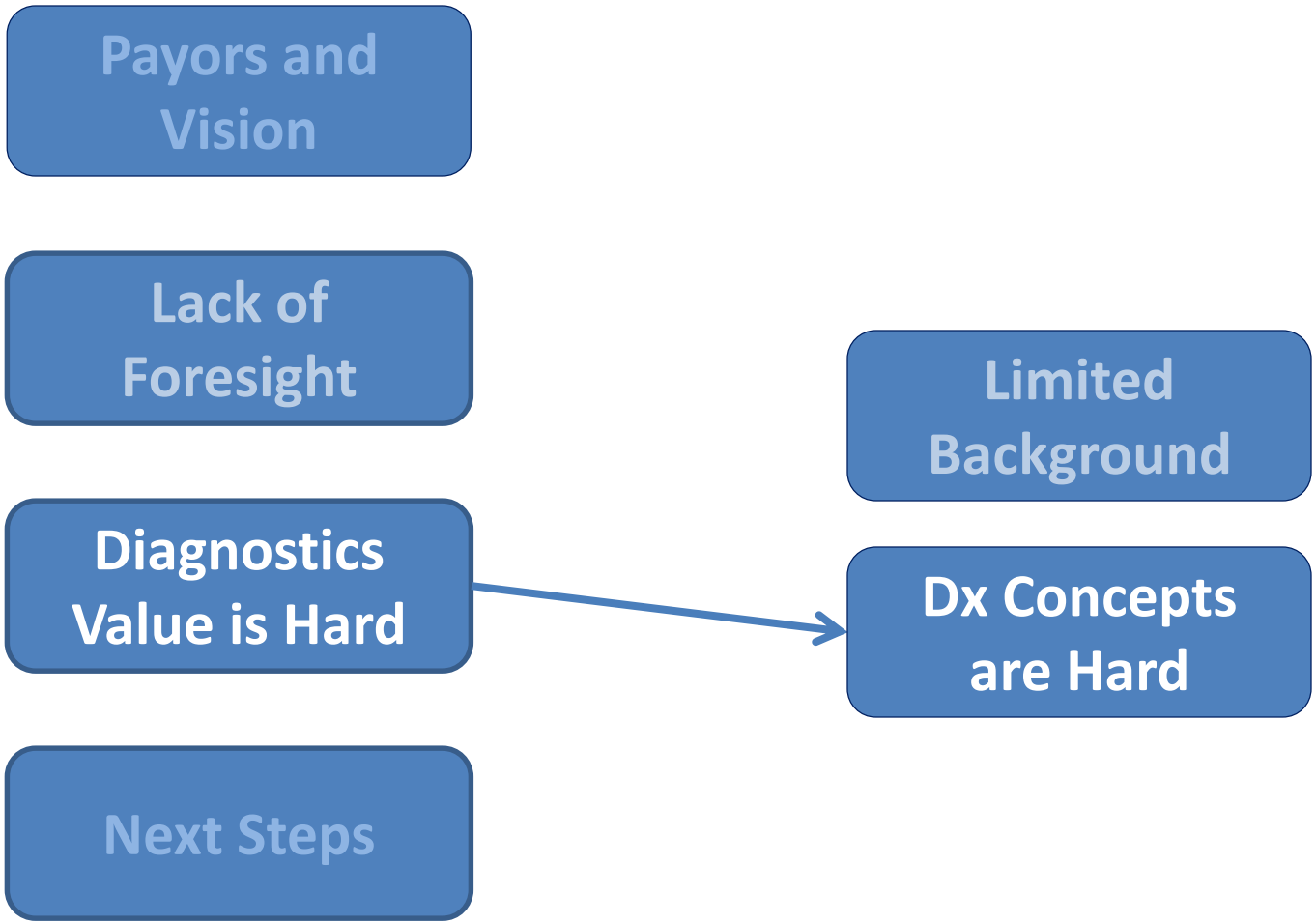

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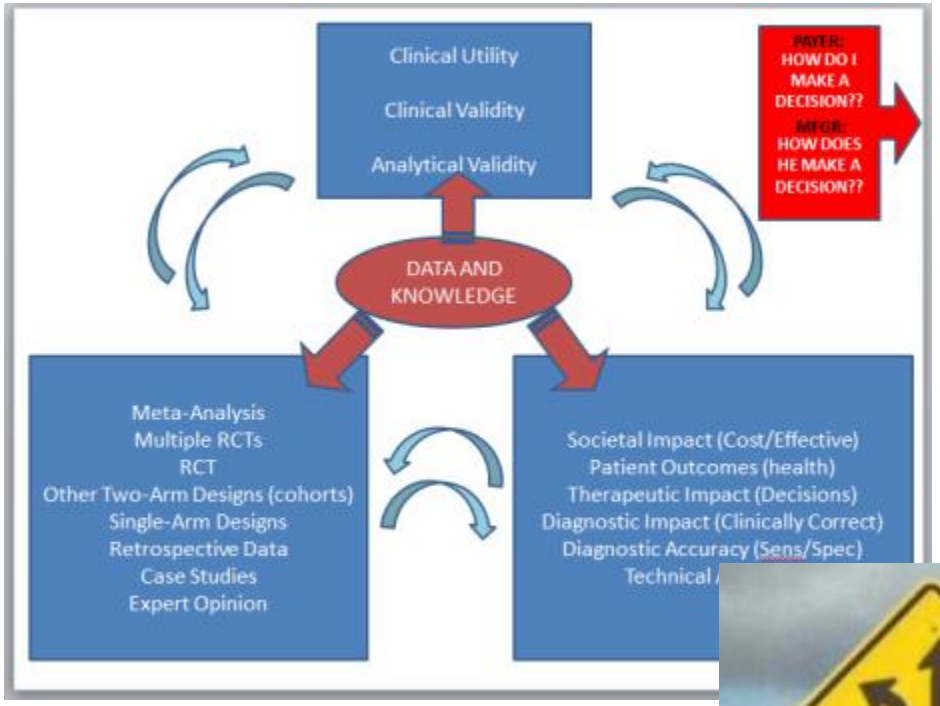
The “Framework” To Date is a Mess



- Nonlinear
- Overlapping Concepts
- No clear path through
- Does not facilitate identification of disagreements

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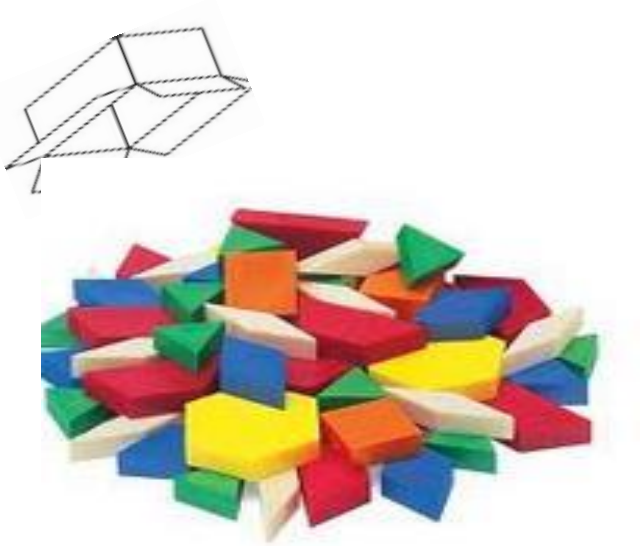
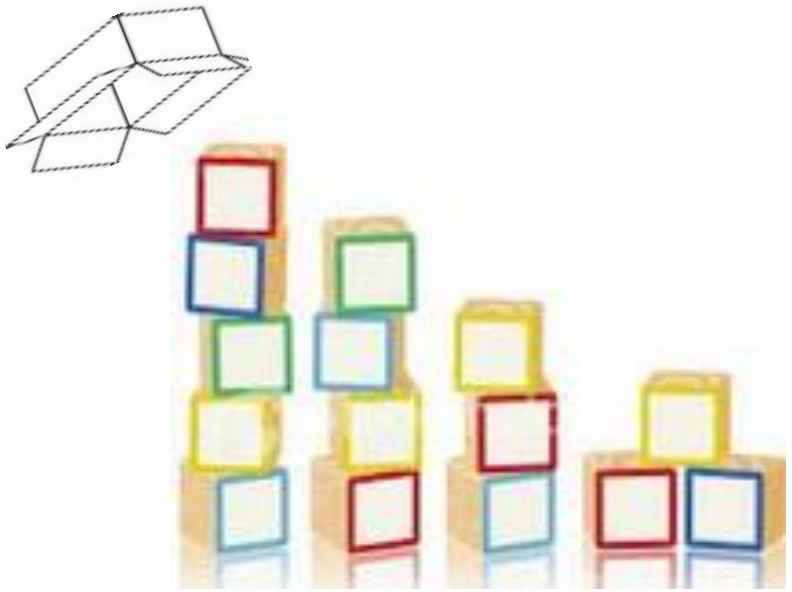
- Test Value & Coverage Negotiations Today



- How we wish they were



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		Diagnostic Tests
❶ Minimal Evaluation Guidance		The test should have analytical validity, clinical validity, and clinical utility.

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	Movies	Diagnostic Tests
❶ Minimal Evaluation Guidance	The movie should have a beginning, middle, and end.	The test should have analytical validity, clinical validity, and clinical utility.

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	Movies	Diagnostic Tests
❶ **Minimal Evaluation Guidance**	**The movie should have a beginning, middle, and end.**	**The test should have analytical validity, clinical validity, and clinical utility.**
❷ **Modular Evaluation Guidance**	• Who is the protagonist? • Is the protagonist sympathetic or unsympathetic? • How are the setting and lead characters introduced? • What main challenge does the protagonist face? • What character development does the protagonist undergo? • What raises tension between the second and third act?	

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	Movies	Diagnostic Tests
❶ **Minimal Evaluation Guidance**	**The movie should have a <u>beginning</u>, <u>middle</u>, and <u>end</u>.**	**The test should have <u>analytical validity</u>, <u>clinical validity</u>, and <u>clinical utility</u>.**
❷ **Modular Evaluation Guidance**	• Who is the protagonist? • Is the protagonist sympathetic or unsympathetic? • How are the setting and lead characters introduced? • What main challenge does the protagonist face? • What character development does the protagonist undergo? • What raises tension between the second and third act?	• Who should be tested and under what circumstances? • What does the test tell us? • Can we act on the information provided by the test? • Will we act on the information provided by the test? • Does the outcome change, in a way we find value in? • Can we afford it? (Is it a *reasonable* value?)

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“Frueh Questions”

- Who should be tested and under what circumstances?
- What does the test tell us?
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http://www.thirdrockventures.com/team_entrepreneur.php

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Definitions of Clinical Utility

- The concept is so basic that definitions tend to be tautological
  - *"Clinical utility is incremental value in medical care"*

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Definitions of Clinical Utility

- The concept is so basic that definitions tend to be tautological
  - *"Clinical utility is incremental value in medical care"*
  - *"Thanks."*

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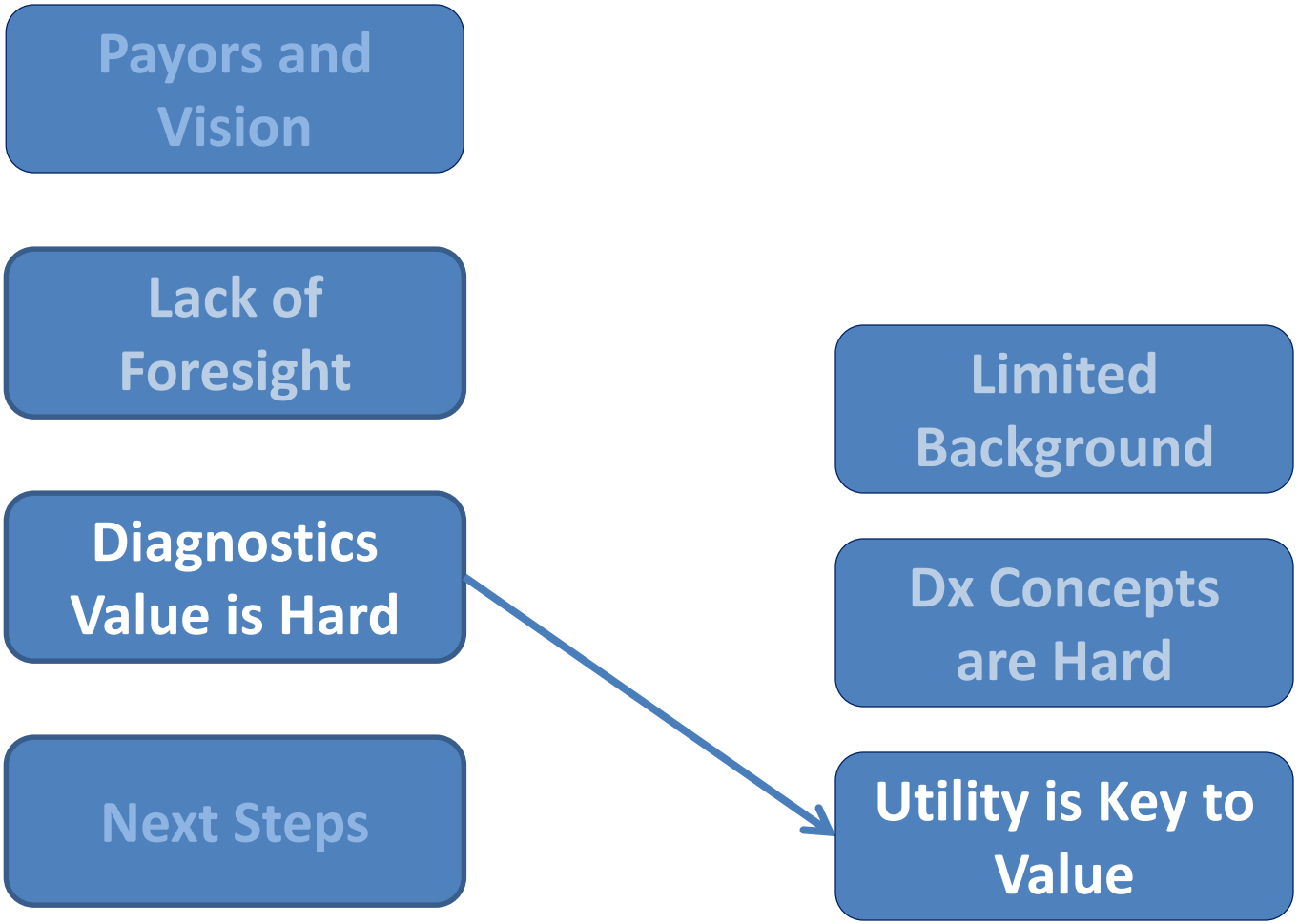

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The Fundamental Theorem of Clinical Utility

Clinical Utility is Always Comparative

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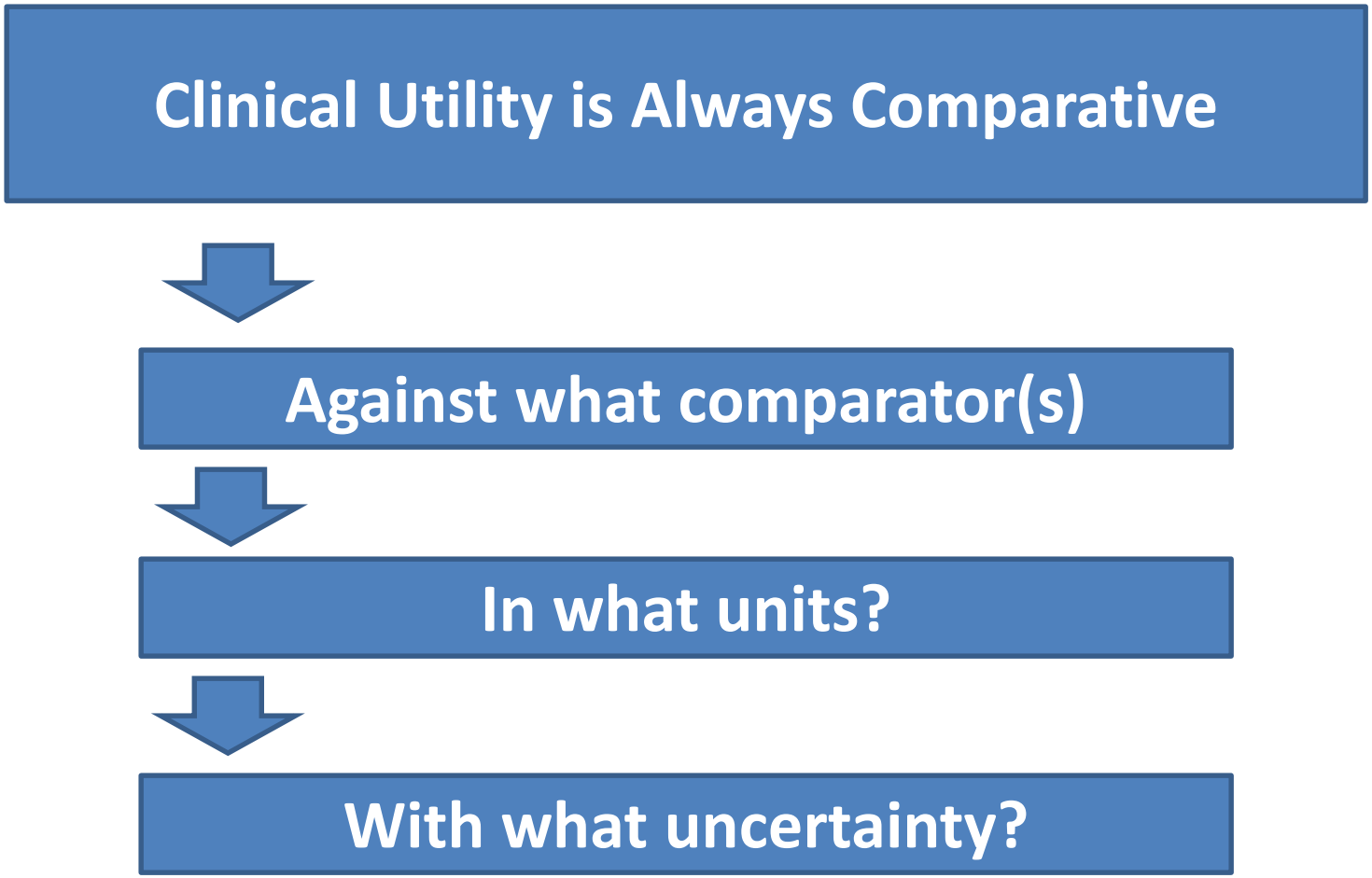
The Fundamental Theorem of Clinical Utility



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Clinical Utility is Always Comparative

Against what comparator(s)

In what units?

With what uncertainty?

Recurrent Issues

- Developer wants most impressive and easiest comparator that's acceptable
- Payers wants most realistic comparators, often seeing multiple scenarios, with the most extensive data (population, duration)

- Comparisons always have direct or implied units, even qualitative ones
- Clinical utility units are diverse: survival, less pain, less adverse events, faster diagnosis, same impact at less cost
- Some units invoke controversy: greater sensitivity (finding tumors that needn't be found?)

- Statistical uncertainty: 50% longer survival, plus minus 10%
- Pragmatic uncertainty: will it work outside the trial, in rural areas, with family MDs (external validity)
- Conceptual uncertainty: it's probably predictive, but may be only prognostic. This biomarker should still be important, although today drugs are different.

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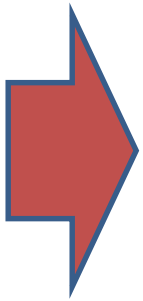
All tests will have clinical validity that is better, in some way,
(information we did not have before the test)



Which causes clinical utility to be better, in some way.
(something happens after the new information)

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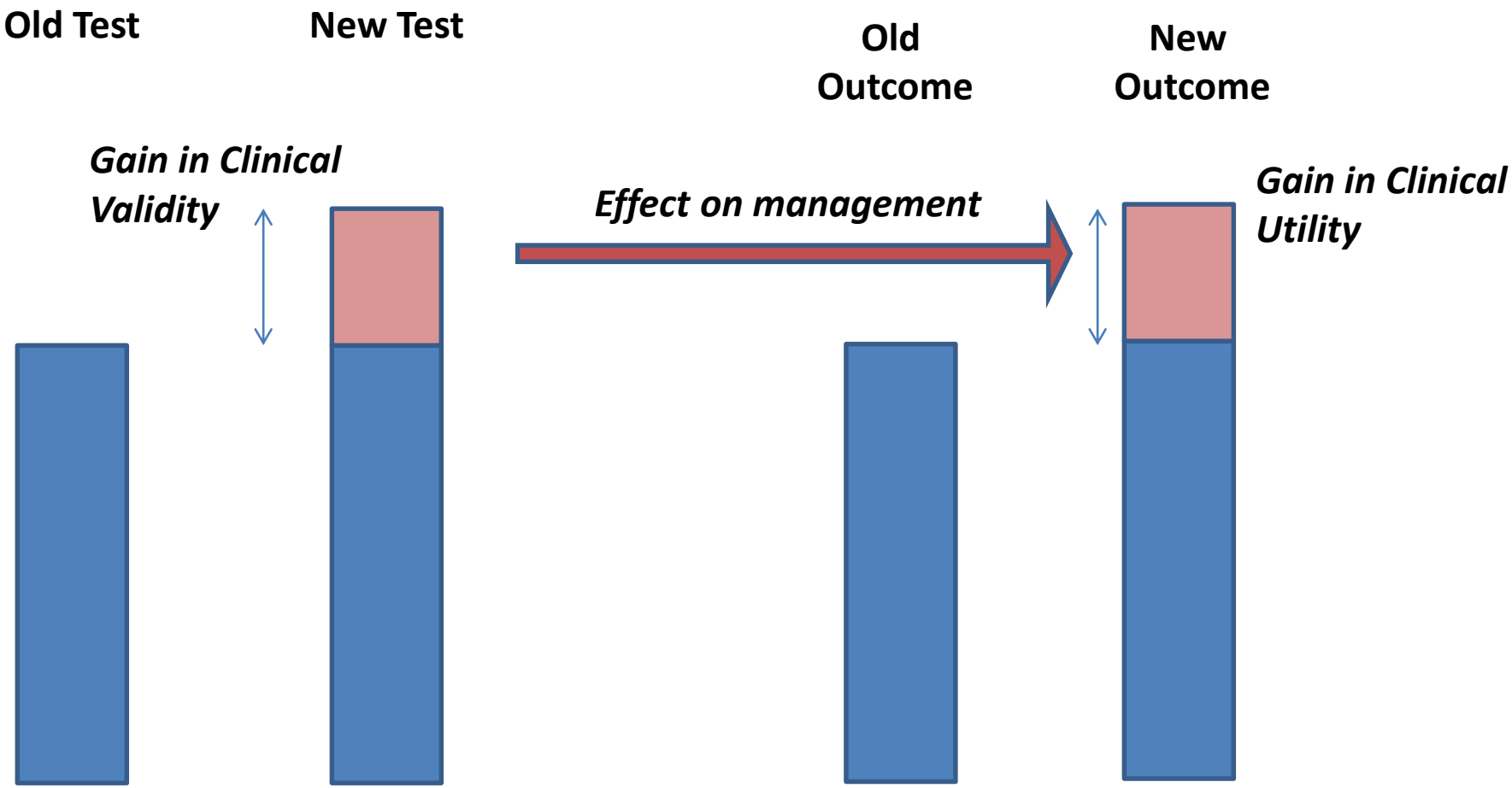

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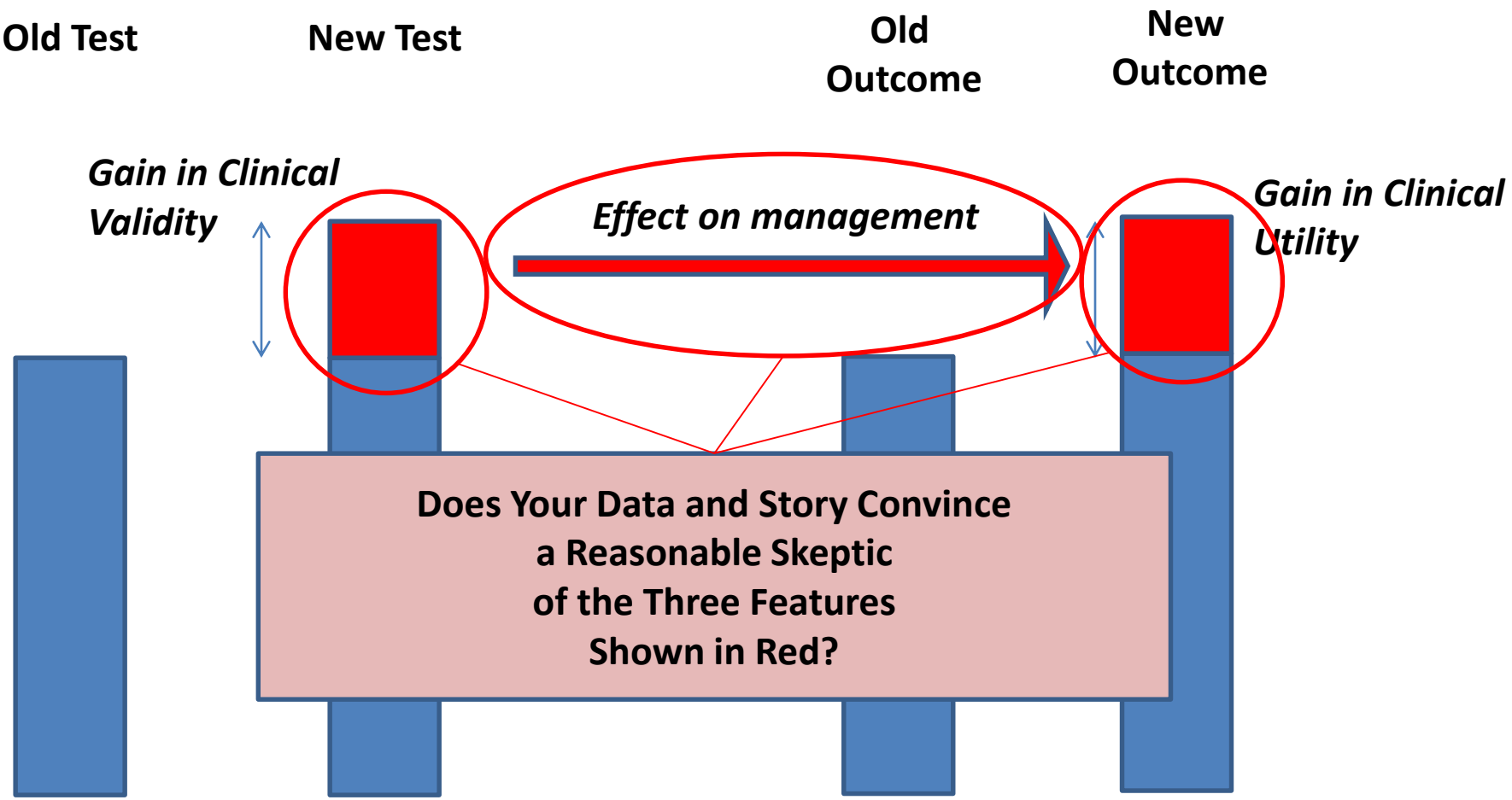

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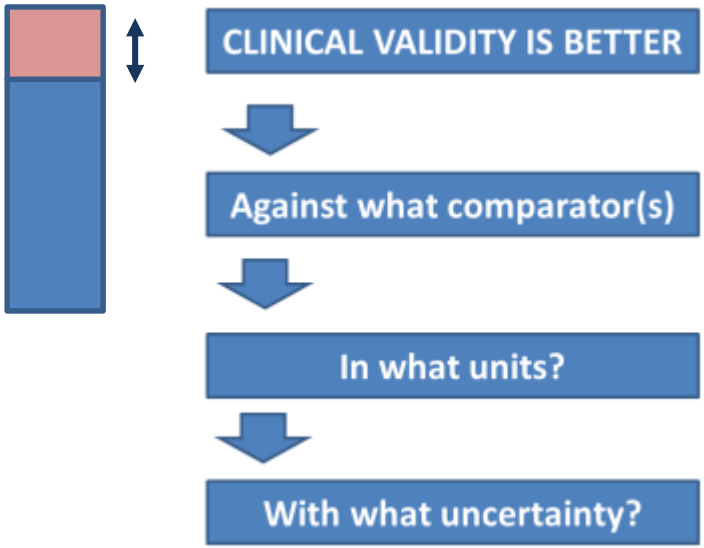

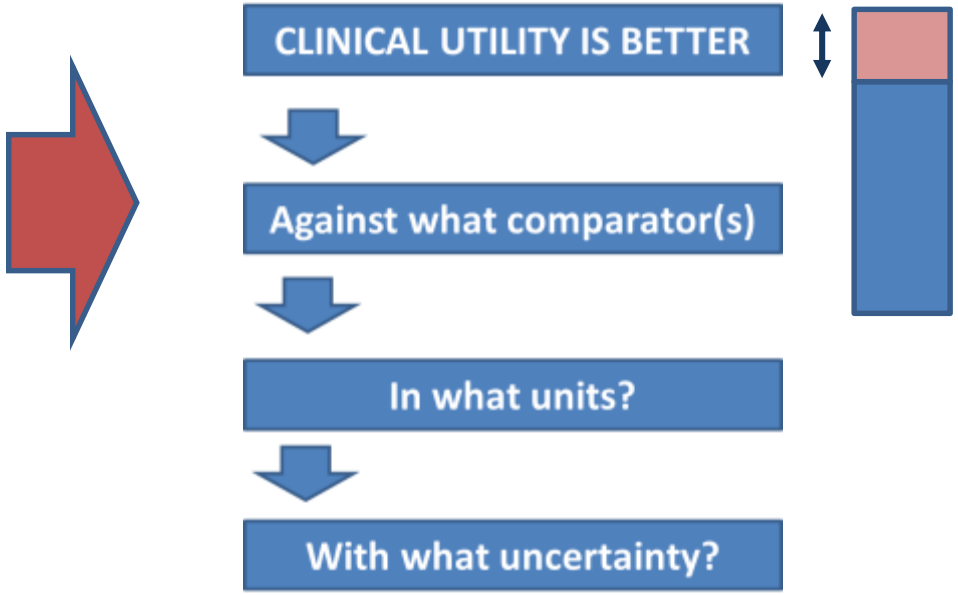

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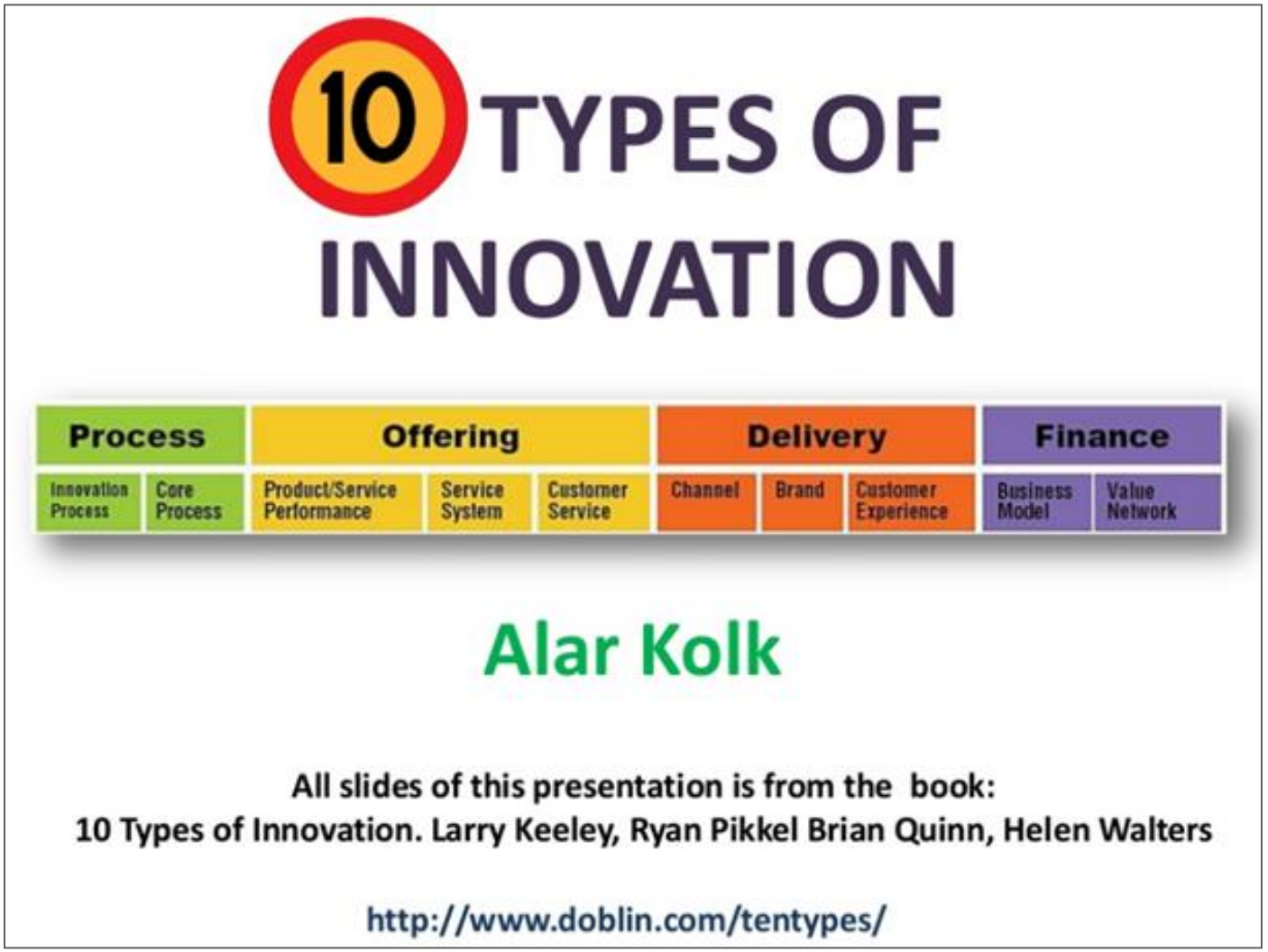
There are a finite number of basic ways to do "innovation…."



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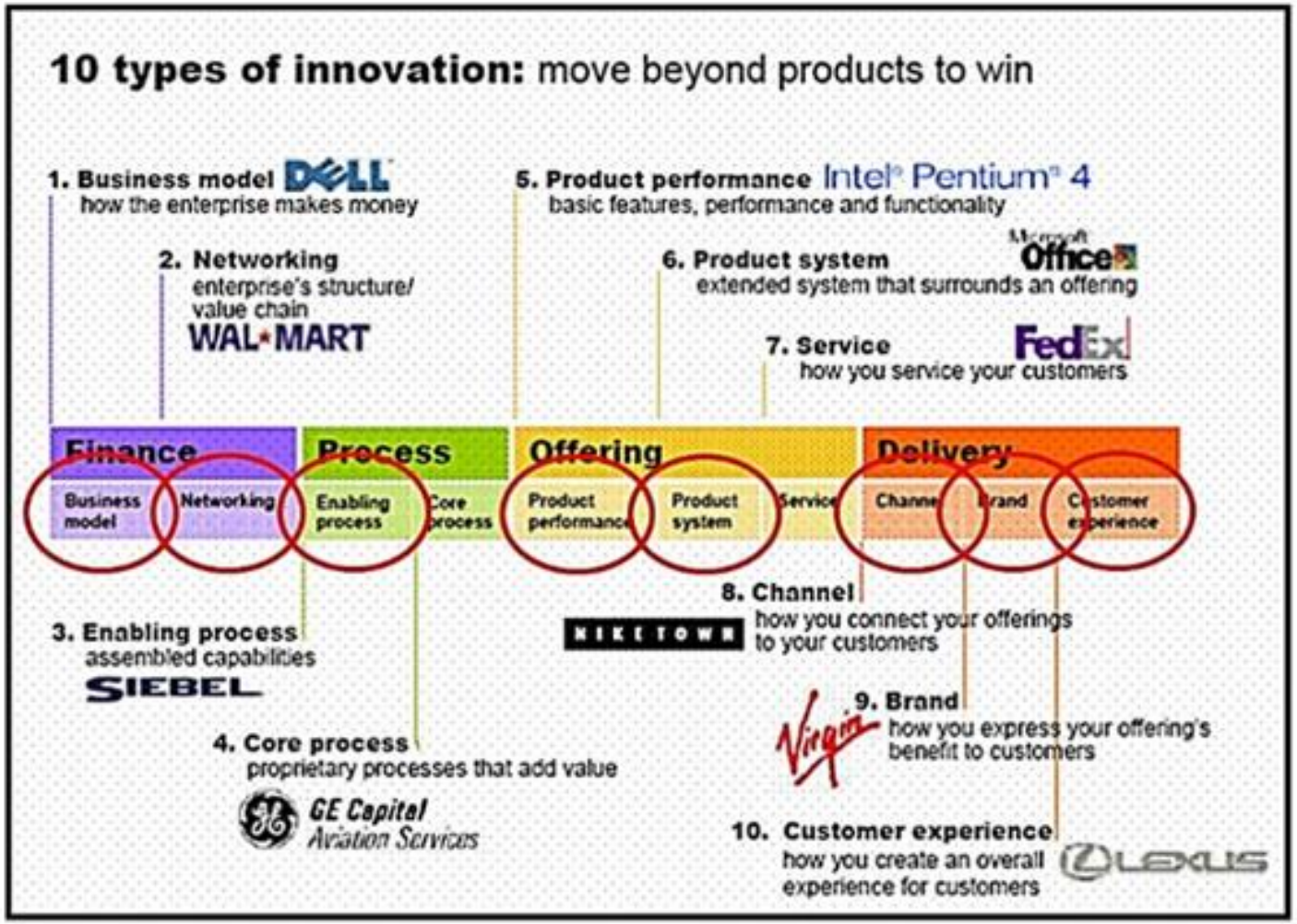
Companies Classified by Type(s) of innovation



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There are a Finite Number of Ways to Improve Clinical Validity

Do exactly the same thing	Better Sens & Spec (Better Accuracy)	Measure Target that is Entirely New	More Accurate Prognosis	Reflex to Resolve an Ambig-uous Test	Diagnosis Where All Other Methods Fail (No gold std)	"RULE OUT" some patients for something

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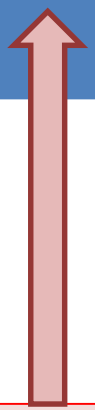
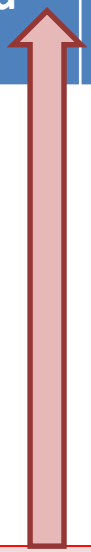


Hard to quantify this!!!
An R value; A P Value; a "Reclassification Index?"
And the "delta" has what clinical impact?



Is it really the same thing?

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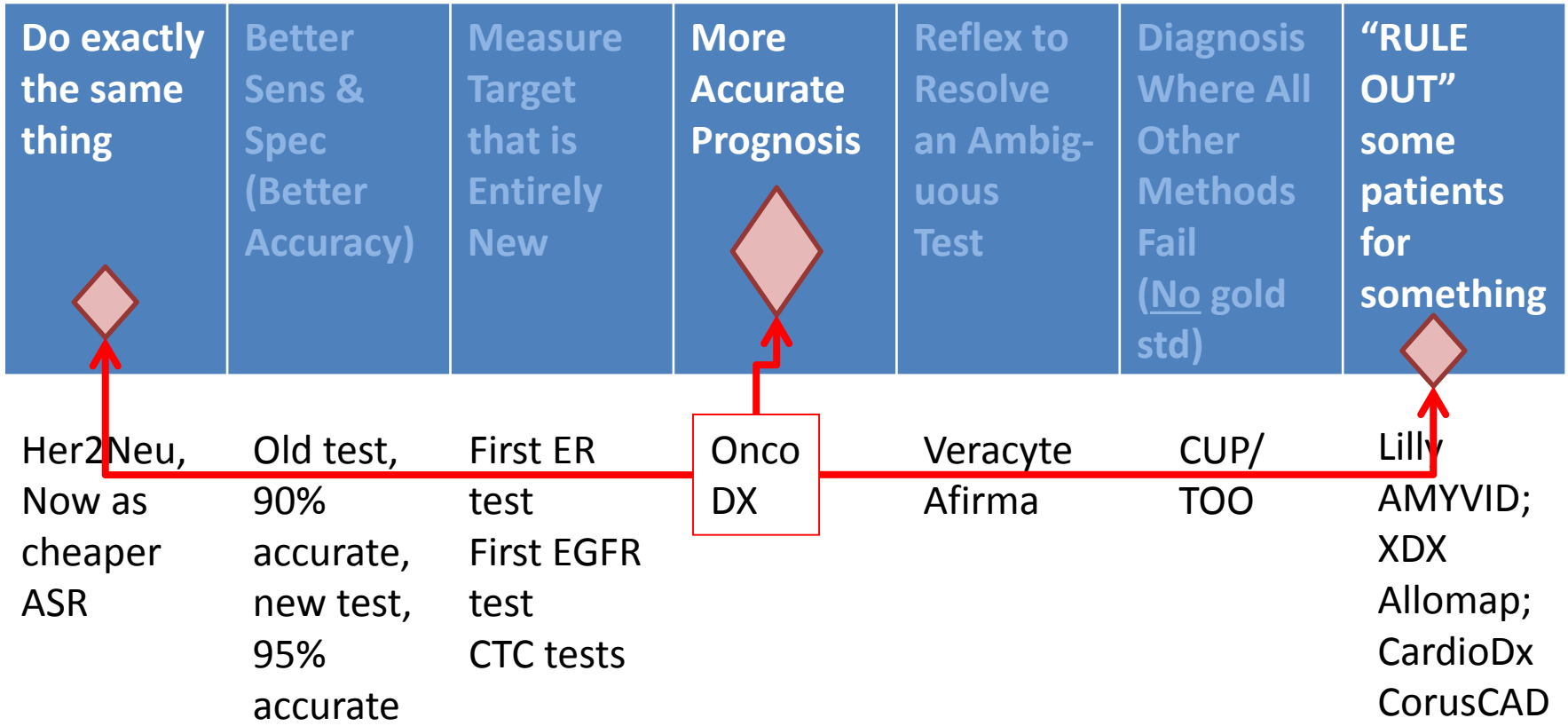

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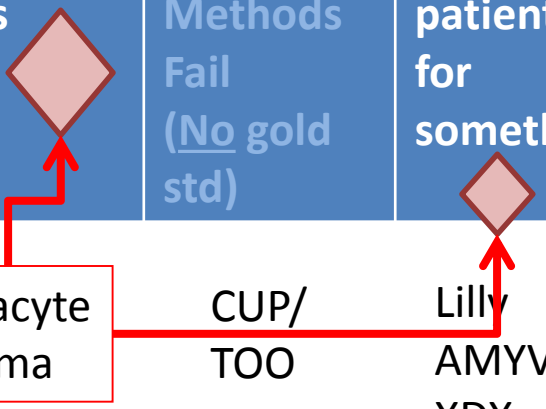

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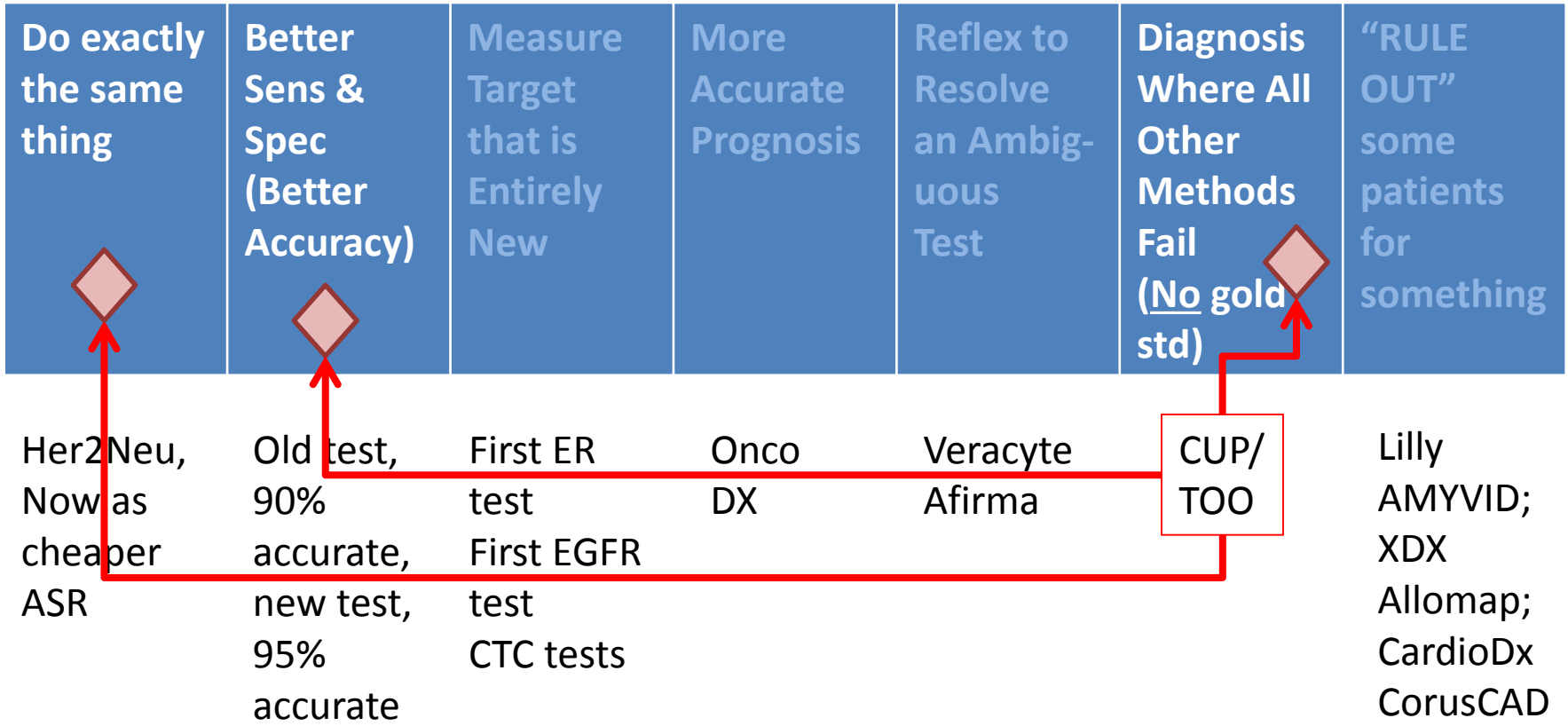

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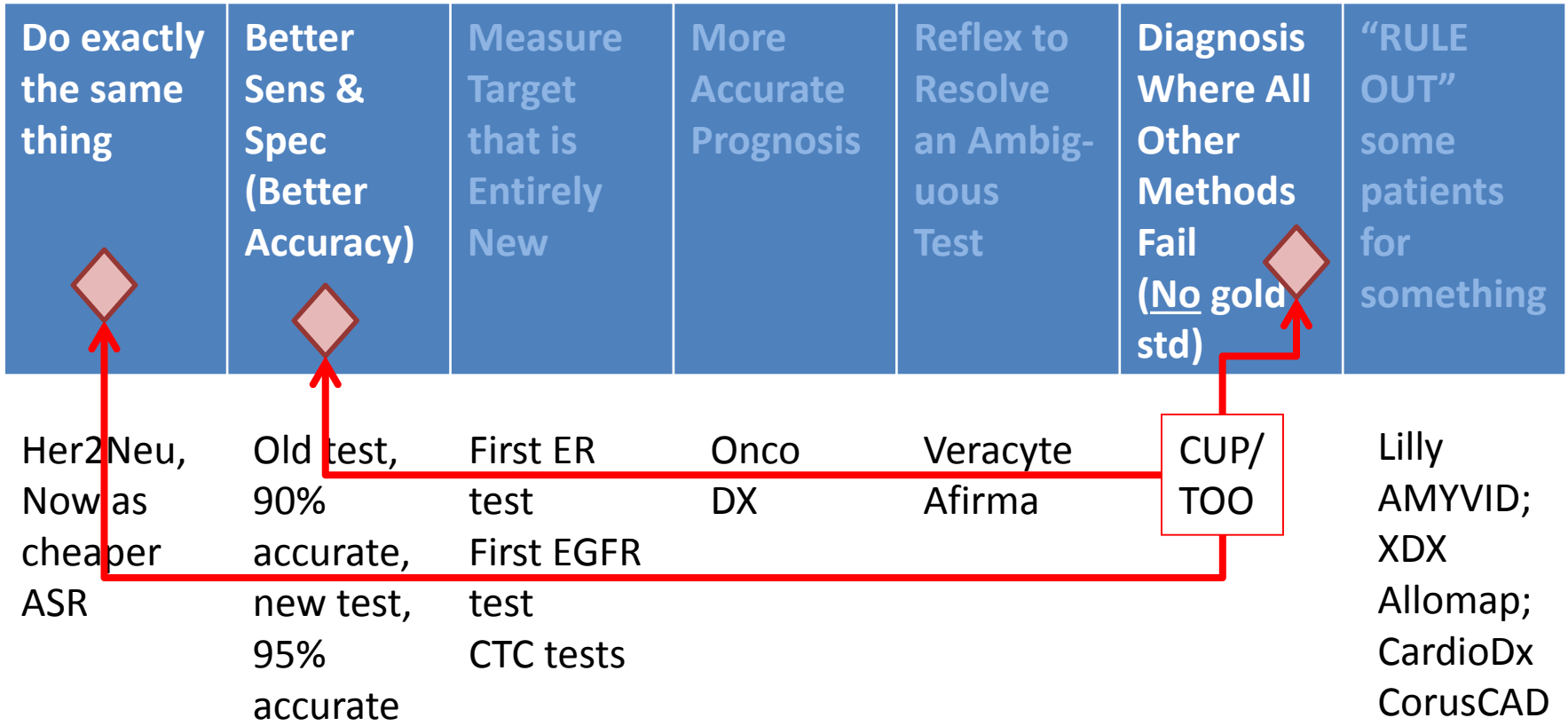

Proponents:

We're doing exactly the same thing we were already trying to do, but doing it faster, better, more accurately

Opponents:

There's no gold standard, and we have no idea what you are doing

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Hard to quantify R value, P Value; Do We Need?

Is it really the same thing?

Corresponding Clinical Utility Questions

"Same Thing, Cheaper"	Easiest if similar price	Drug Combi Dx here	Mgt Pathway? Risk?	Same as if prior test had worked	Is it right? What do you "do"?	Really? How often? Is it safe?

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But wait.

- What people probably mean when they actually talk about "**defining clinical utility**"

- is

- Where the **border areas or gray areas** of the concept are…

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- Survival
- Unnecessary surgery avoided
- More effective drug chosen
- Ineffective drug avoided
- Less pain
- Faster recovery

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- Biomarkers
- Imaging

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- Diagnosis (per se)
- Value of knowing
- Ability to plan
- Caregiver has better grasp of prognosis

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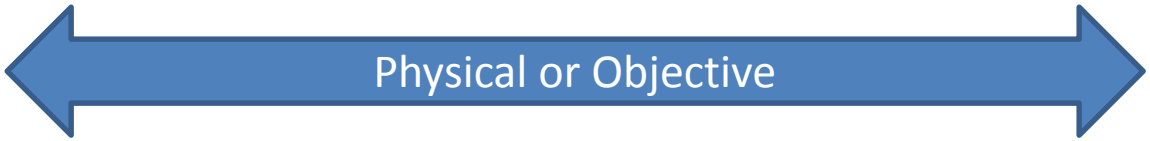

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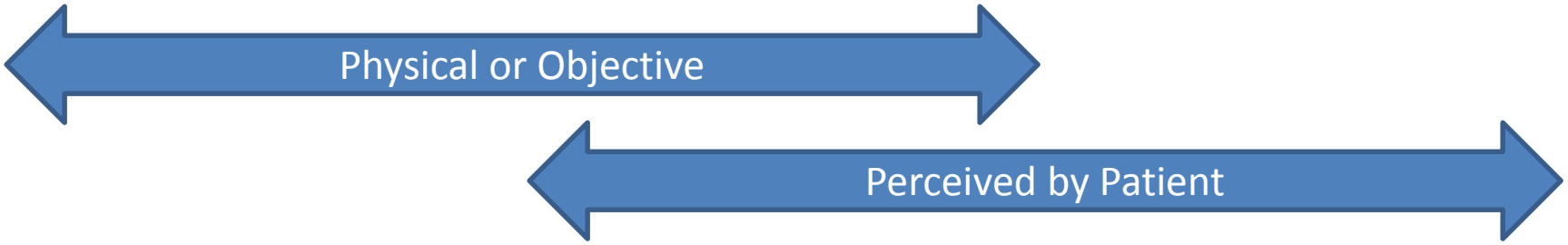

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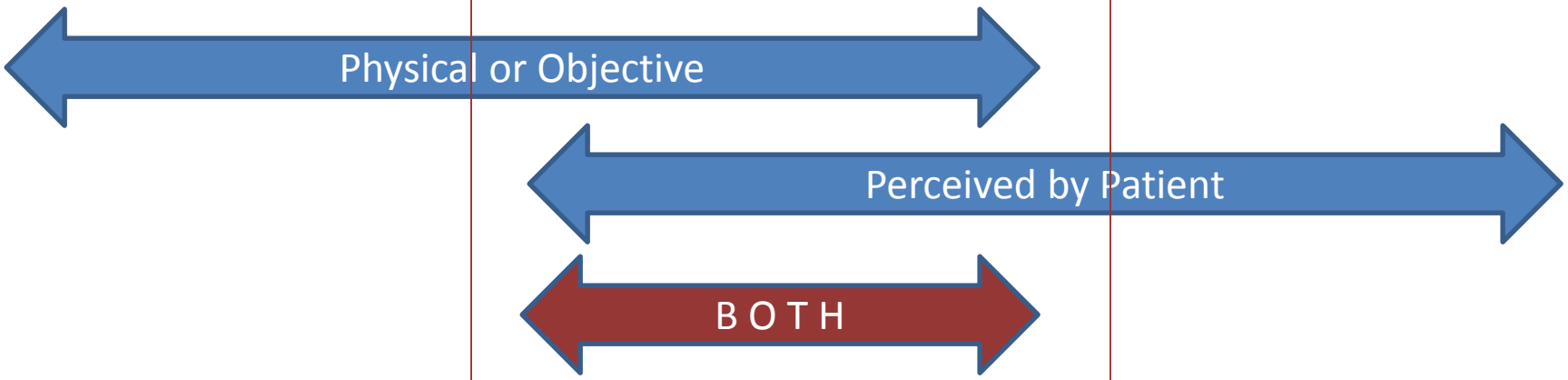

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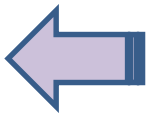
In fact, there are gray areas.

- Biomarkers
- Imaging



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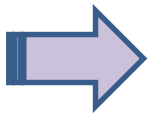

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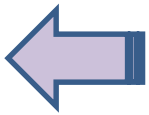
In fact, there are gray areas.

- HIV viral load is an accepted surrogate biomarker.
- Complete pathological response = no further ChemoTx

- *Full work up for A.L.S. (no treatment for it)*
- *Breast implants post mastectomy (CMS NCD) – what medical "function of the organ" is being restored?*
- *Cataract surgery (is being able to read or watch tv a "medical benefit?")*
- *Psychotherapy for mental illness (anxiety)*

- Biomarkers
- Imaging



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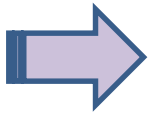

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A word on RCTs for Outcomes in Diagnostics

1. **Generally VERY inefficient when pivoted on the diagnostic**
   - E.g. 100 patients with conventional care, 100 patients get Herceptist.
     - 20 patients are Her2neu positive, 10 respond to Herceptin, and 90 patients in both arms have the SAME outcome, washing out effect
     - Similarly: Warfarin genetics, only top and bottom 10% impact outcomes
2. **Ethics**
   - Pre-RCT data may be 80% or 85% convincing
3. **Can't do "ideal" study – no double blind trial (ridiculous)**
4. **Poor intellectual property boundaries (re-use of IP)**
   - Say: Four companies make allergen IgE tests
   - Payors say not enough data - One company spends $20M on trials
   - Probably will be extended to all four companies
   - Oncotype DX/ Nanostring ProSigna -- ????? - is test more like a "drug" or more like a "PET scanner"?

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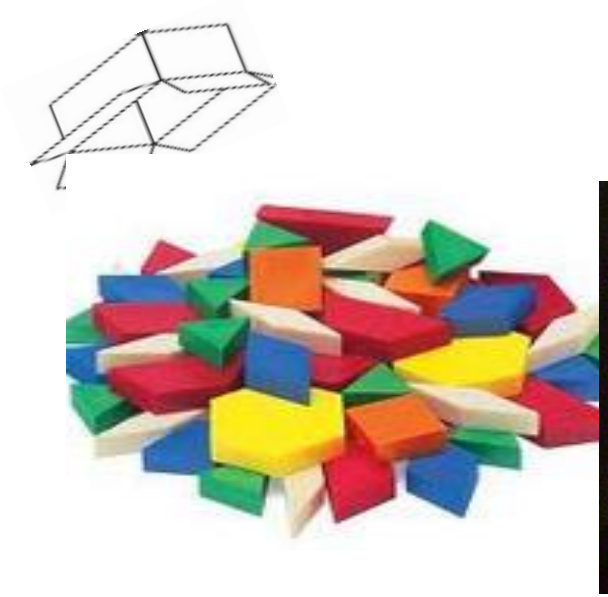
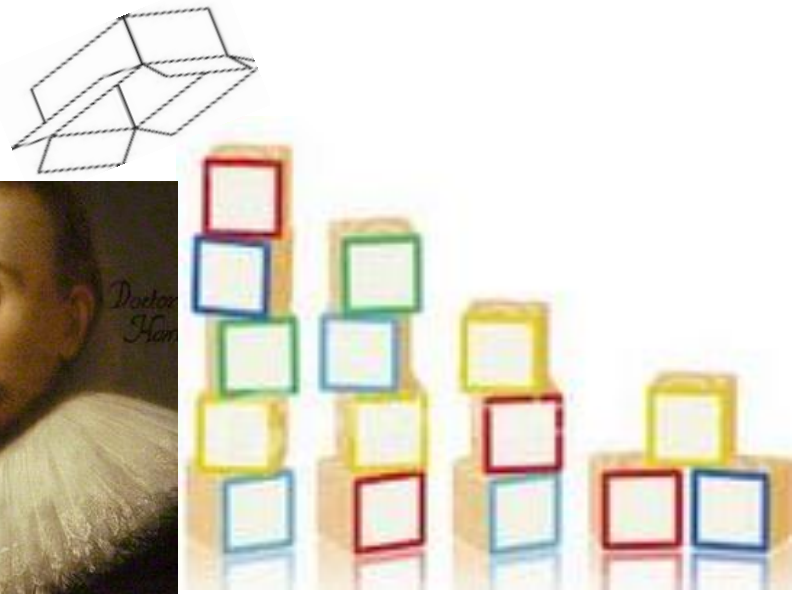
- Test Value & Coverage Negotiations Today



- How we wish they were



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Playing the Right Game

- Your test lacks sufficient clinical utility.
- So…
- So you need more clinical utility.

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Playing the Right Game

- Your test lacks sufficient clinical utility.
- So…
- So you need more clinical utility.

- I understand the value proposition of your test (30% of surgeries will be safely avoided), but I'm not convinced it will happen.

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Playing the Right Game

- Your test lacks sufficient clinical utility.
- So…
- So you need more clinical utility.

- I understand the value proposition of your test (30% of surgeries will be safely avoided), but I'm not convinced it will happen.
- **I'm uncertain because of A,B,C.**
- **This could be addressed by A,B,C.**

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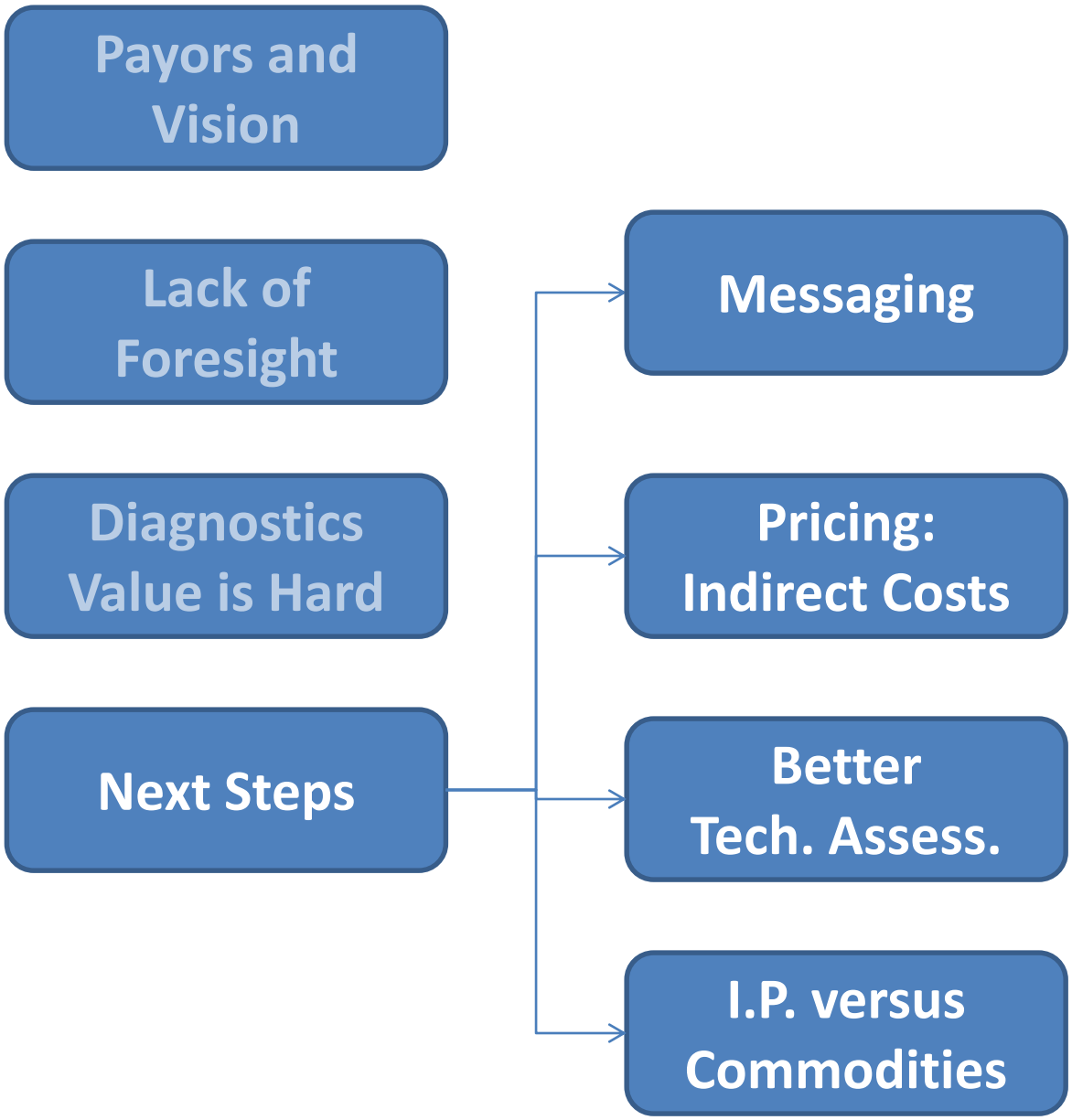

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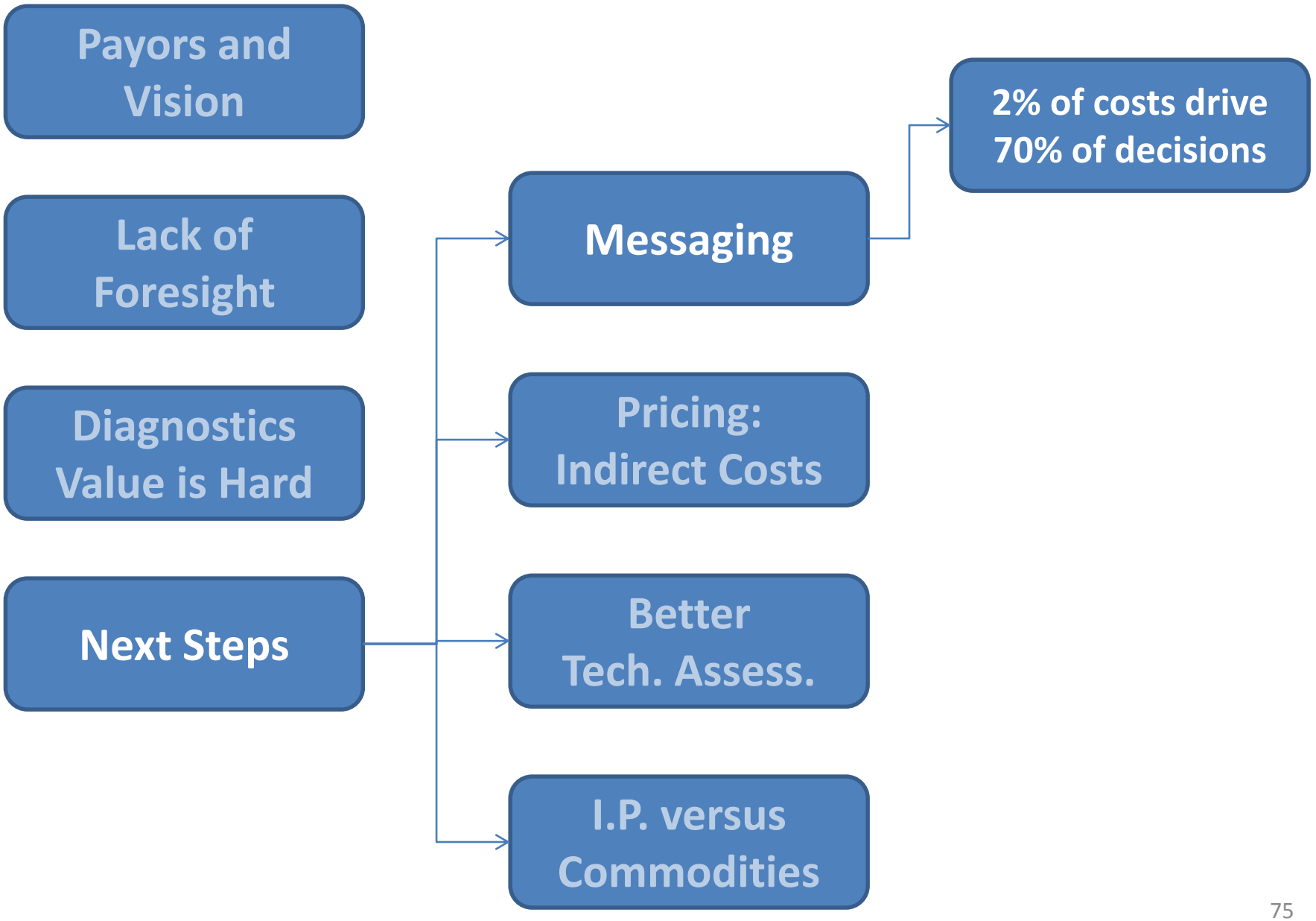

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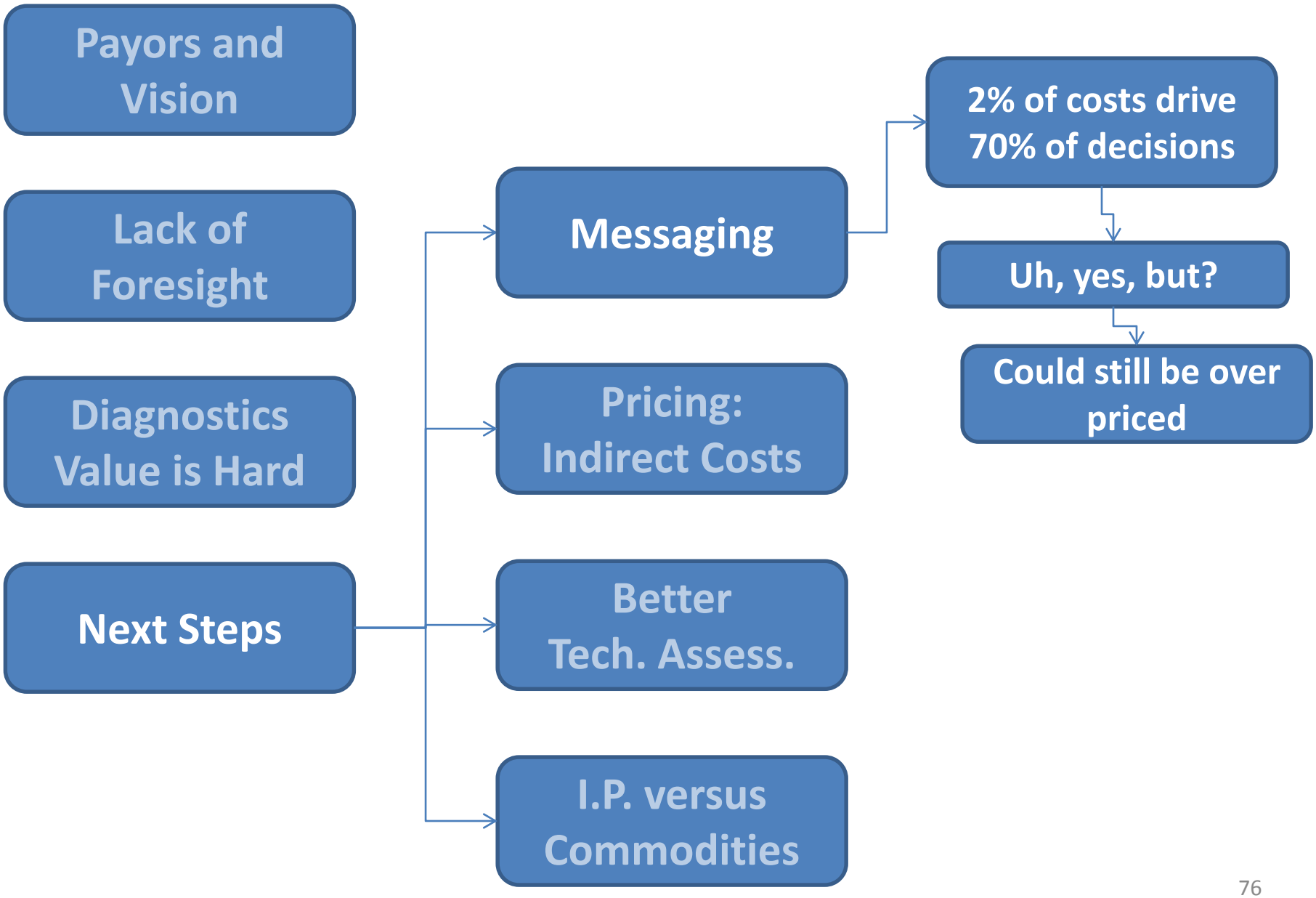

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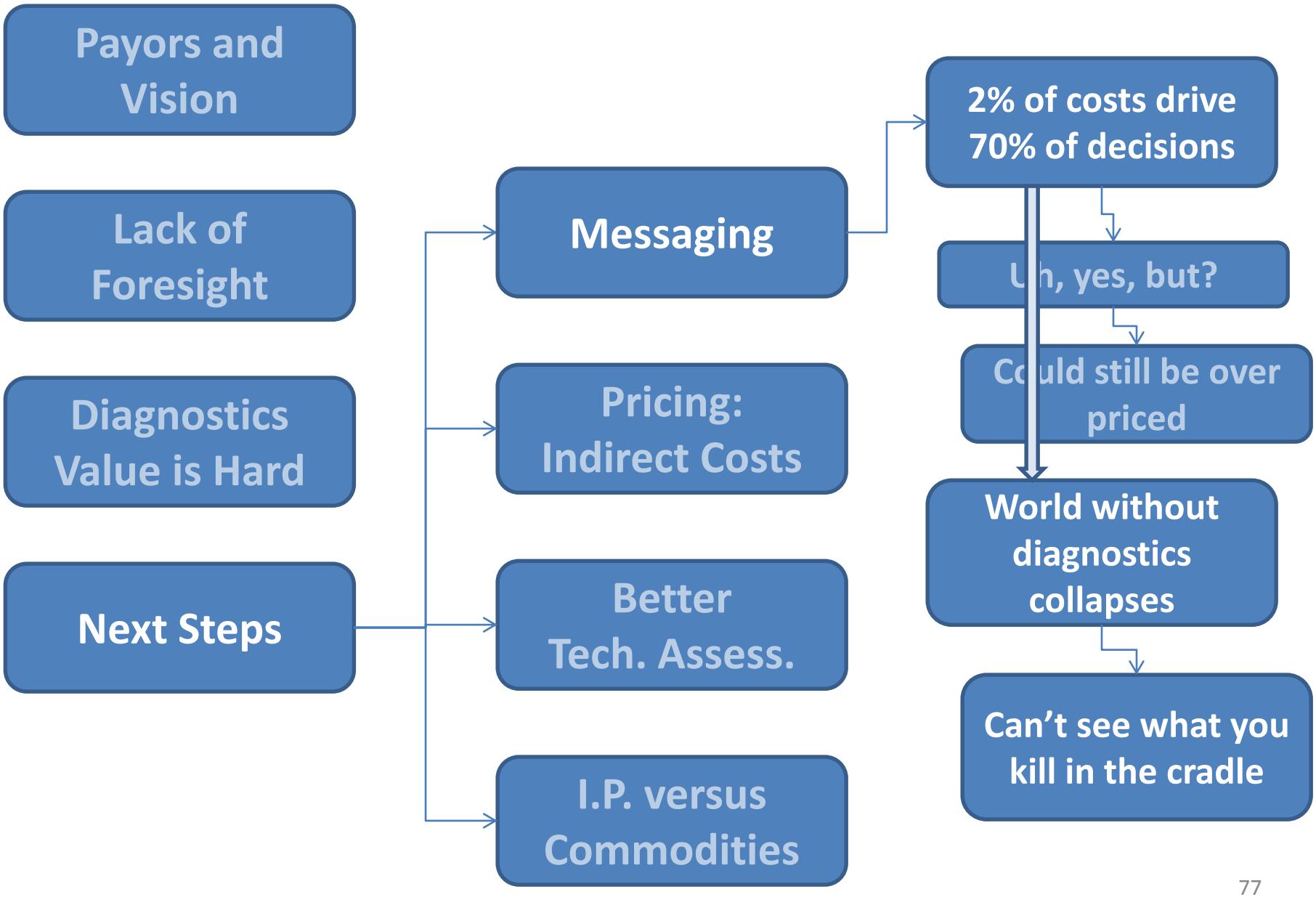

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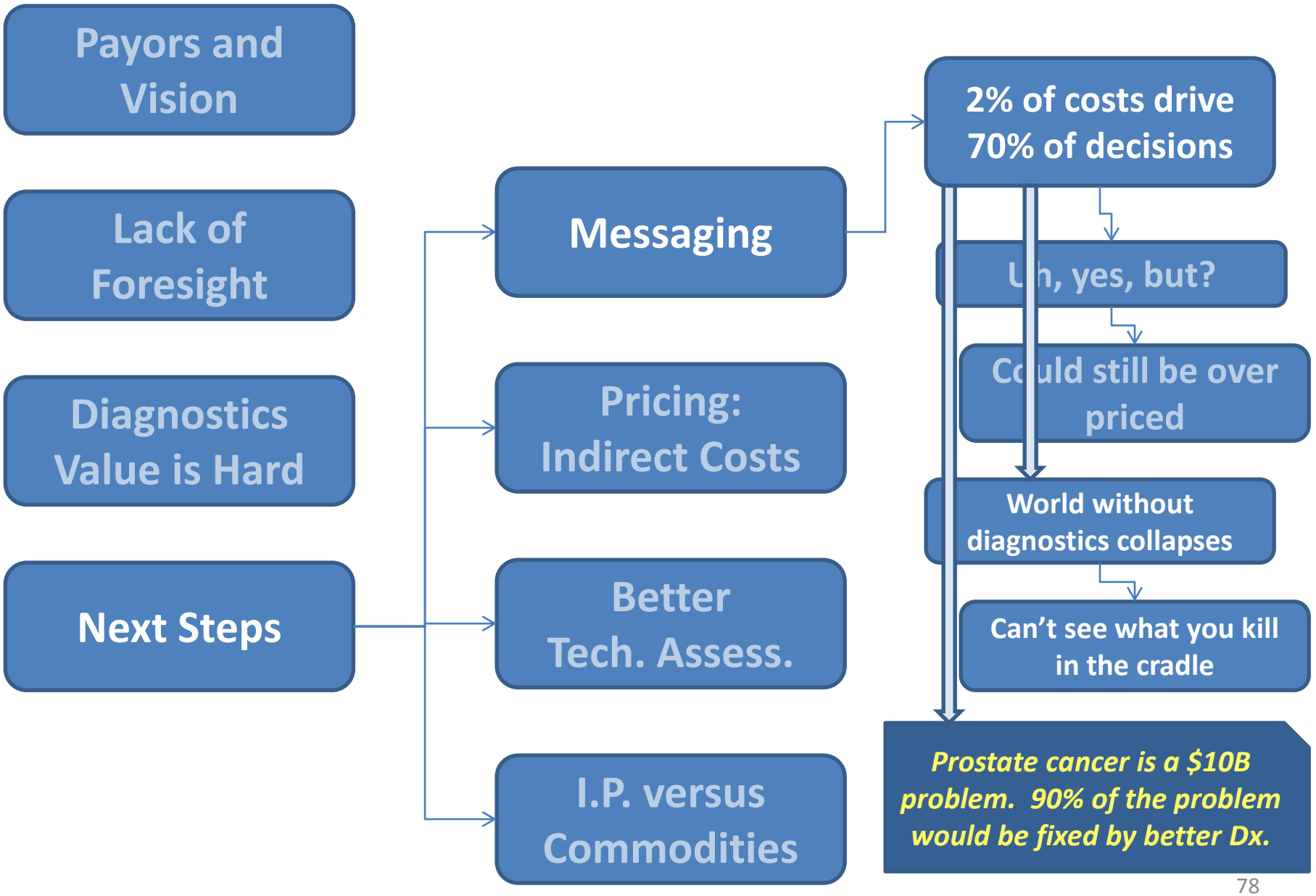

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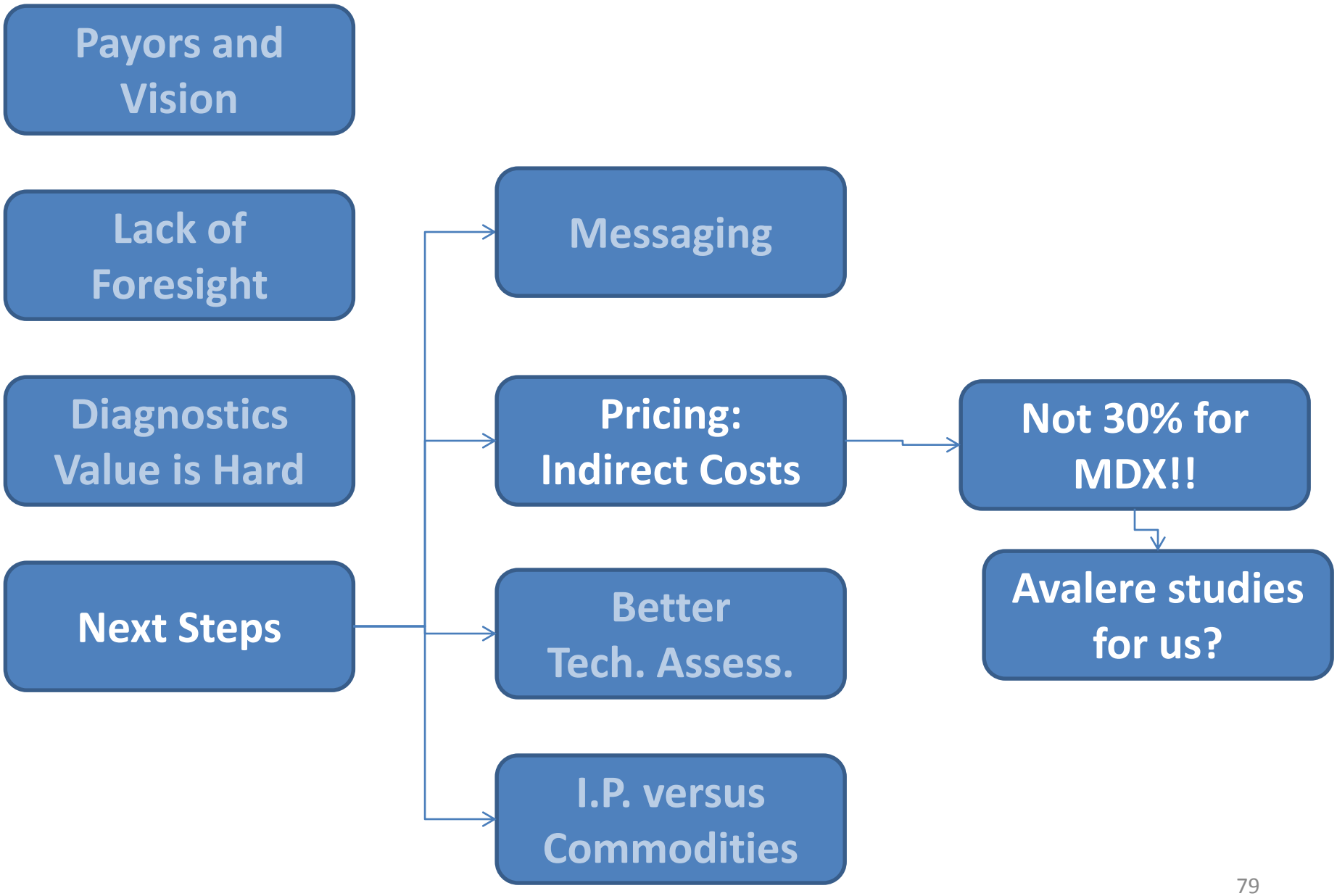

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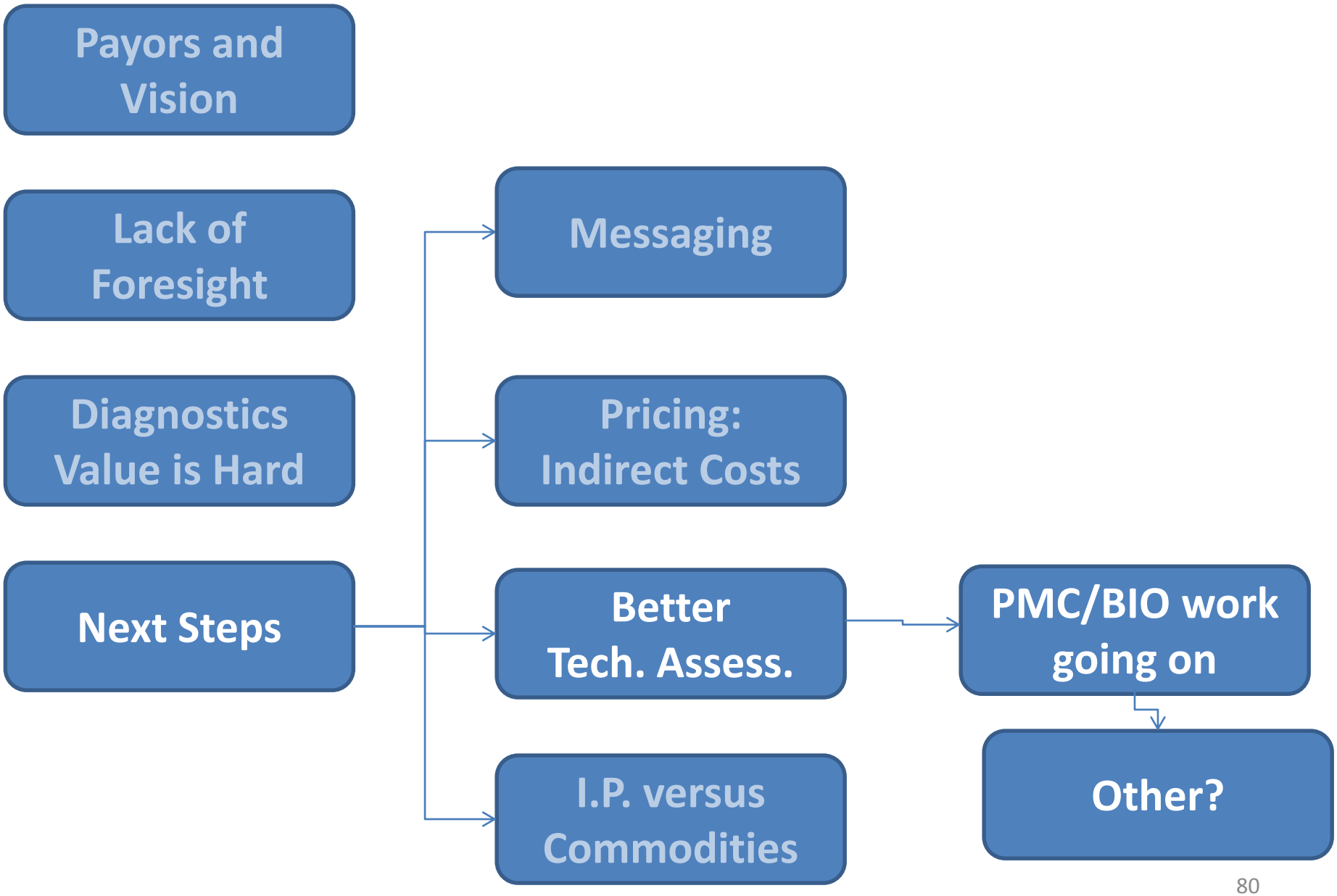

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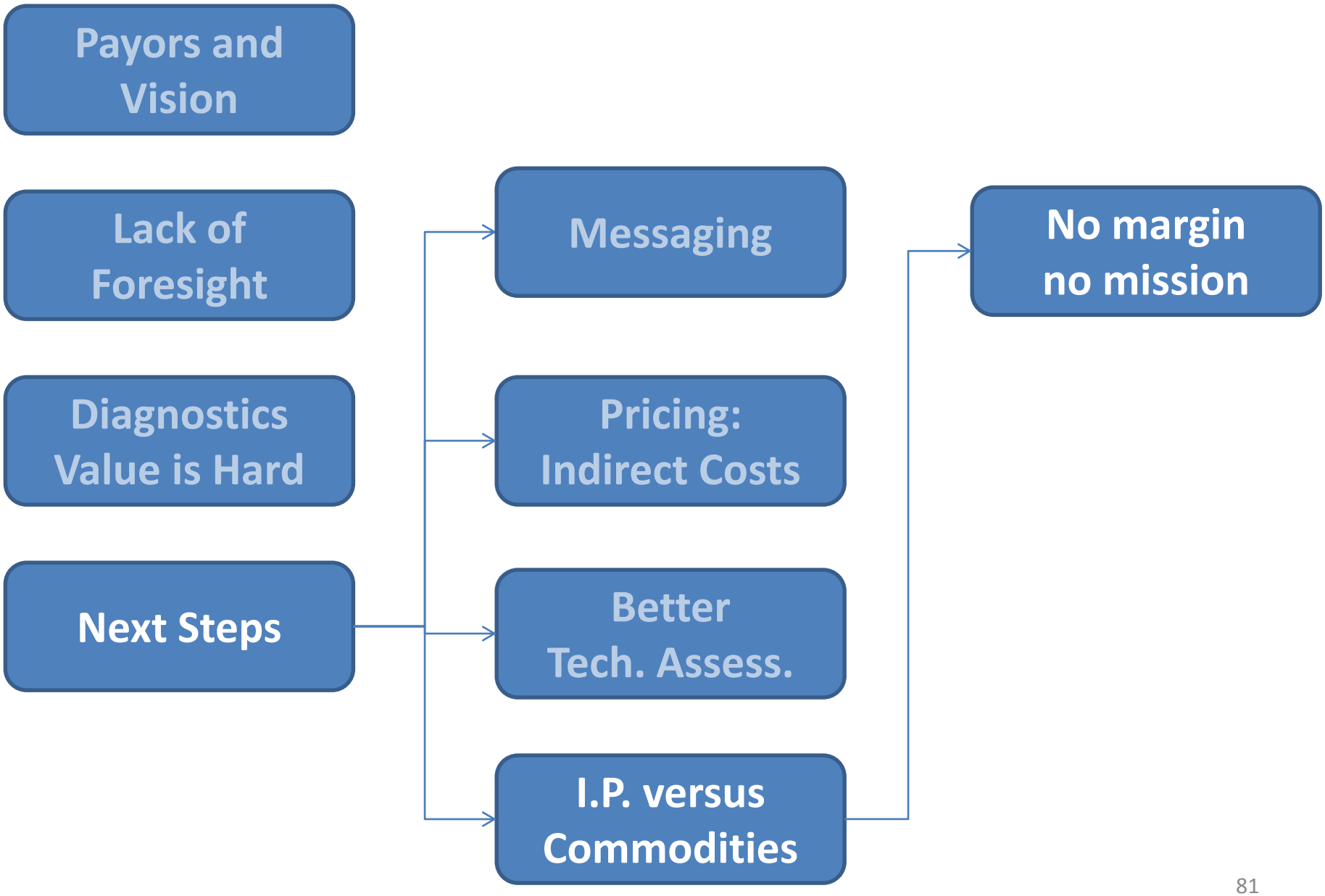

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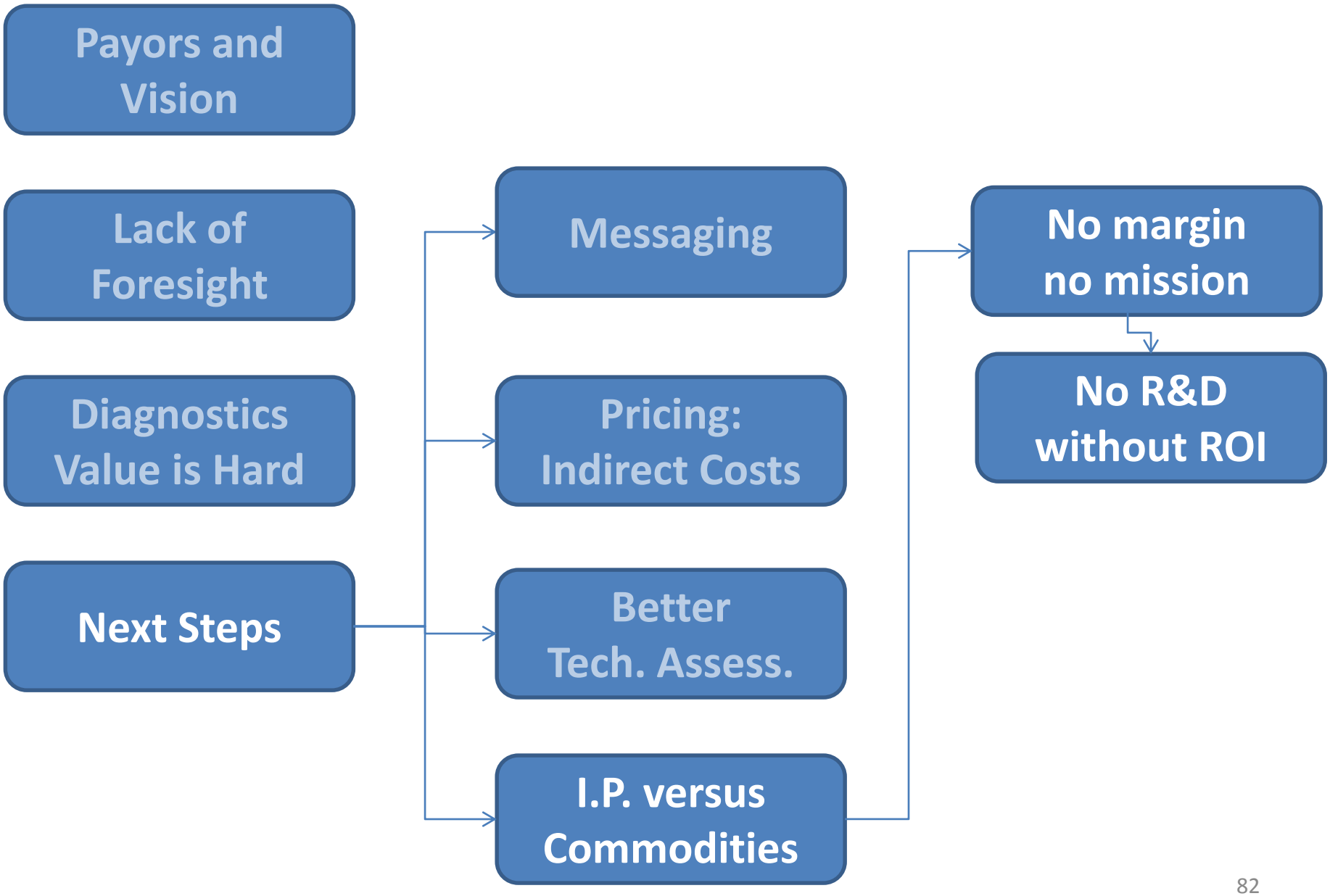

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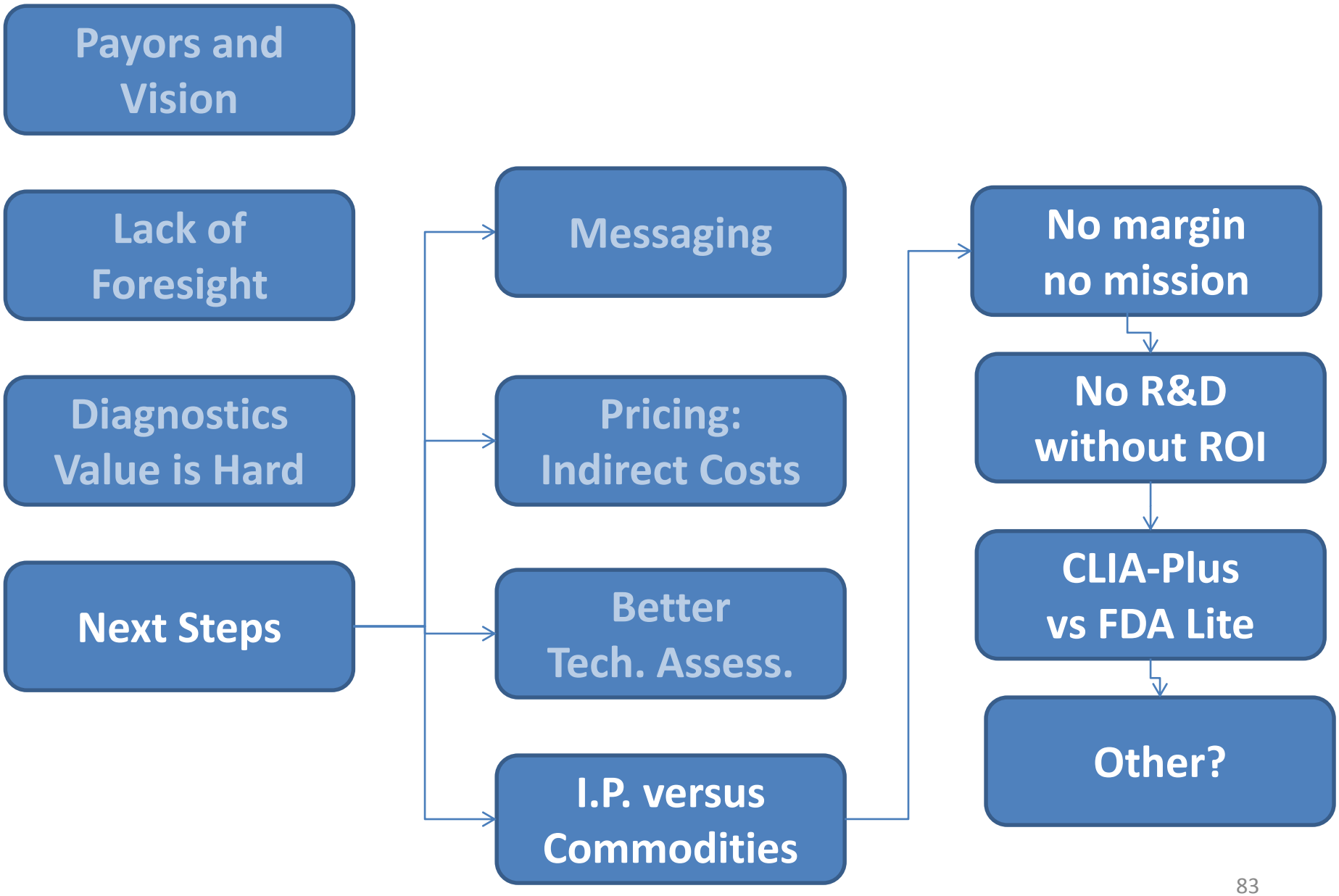

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Bottom Line

- Payors can learn to encourage innovation in the right ways
- If we assessed clinical utility better, we could argue valuation better
  - We have to get better valuation, ergo, we have to assess clinical utility better
- The stakeholder system has to encompass commercial payers, Medicare, Medicaid in a more rational way

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THANK YOU

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The Ascent of Reimbursement

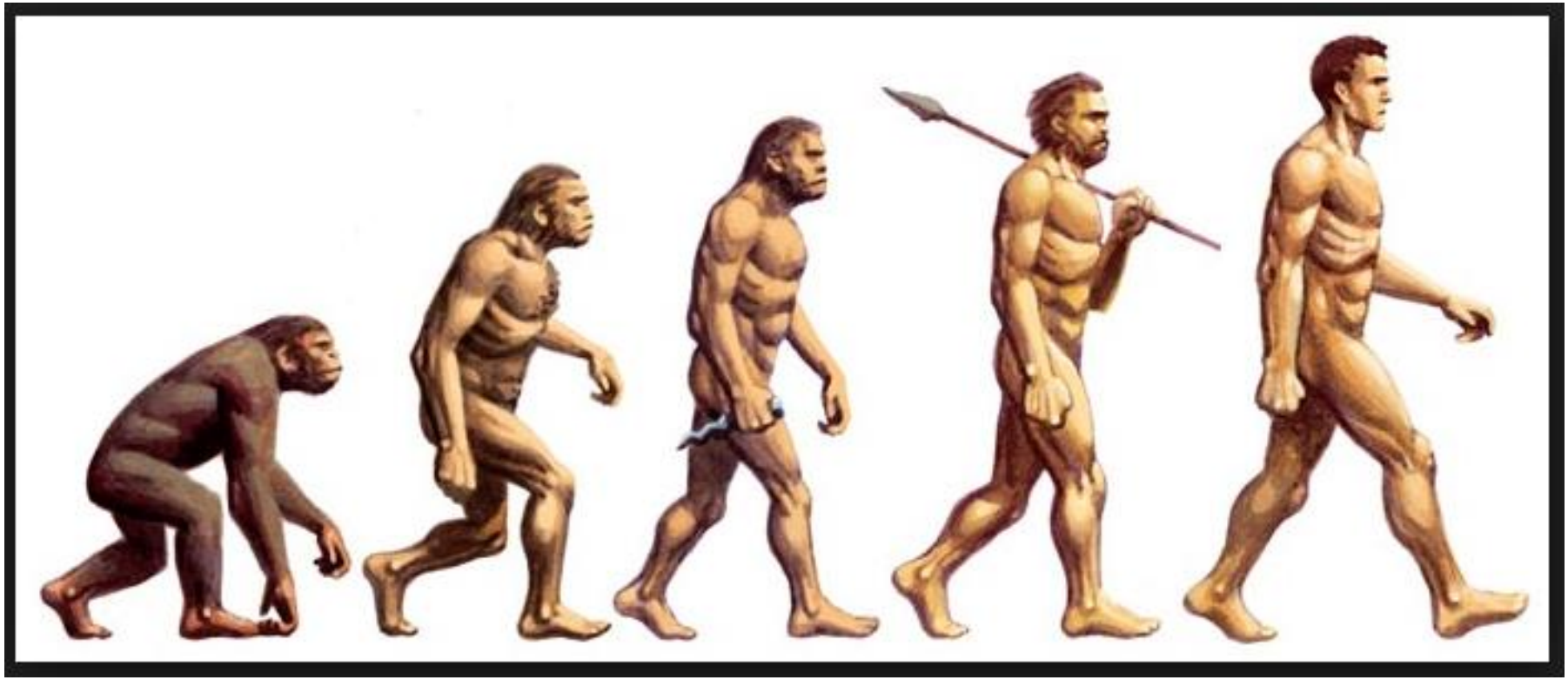
**If we have a code,
They have to pay it.**

**We have to
document clinical validity.**

**We have to have
KOLs send letters.**

**We have to write a
dossier.**

**Clinical Utility is
demonstrated to
impact patient care.**



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