Building the Diagnostic Center at UTMB for All of Healthcare

Michael Laposata, M.D., Ph.D.
Professor and Chairman
Department of Pathology
University of Texas Medical Branch
Galveston

utmb Health

Disclosures

Director of John Sealy Diagnostic Center at UTMB

Scientific Advisory Board For Werfen

Founding member of Expert Diagnostic Colleague

Outline of the Presentation

The state of affairs in Diagnostic Medicine in the US

The recognition of the problem and the assessment of its severity

The challenges in fixing the problem

Attempts to provide a solution

Current activities to create a solution for millions of patients experiencing diagnostic mistakes

The State of Affairs in Diagnostic Medicine in the US

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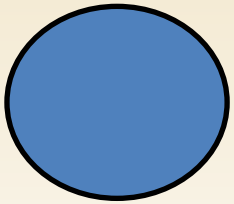
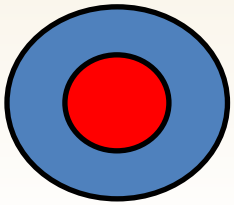
How Much Information is There to Know?

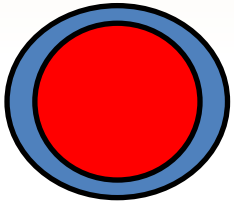
1950



Amount of knowledge available about disease

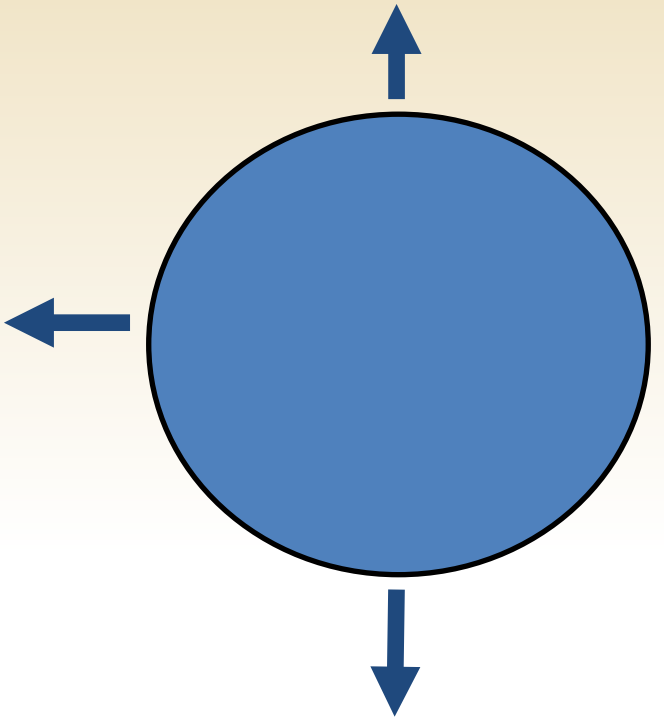


Doctor does not know much about diagnosis

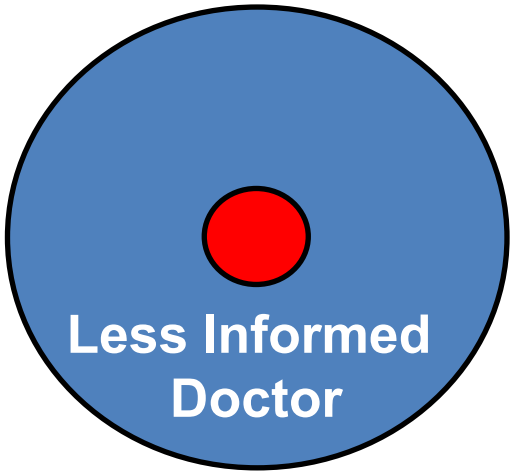


Doctor knows much about diagnosis

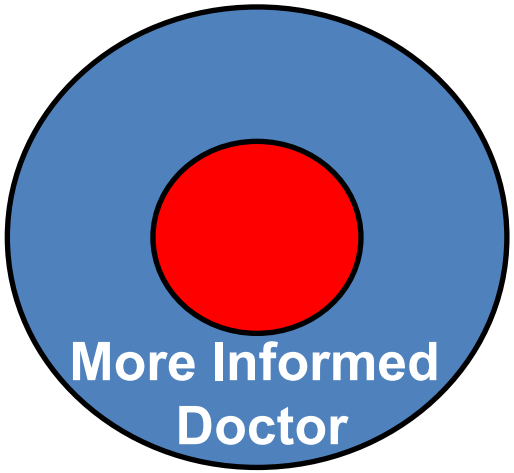
Today



Amount of knowledge available about disease

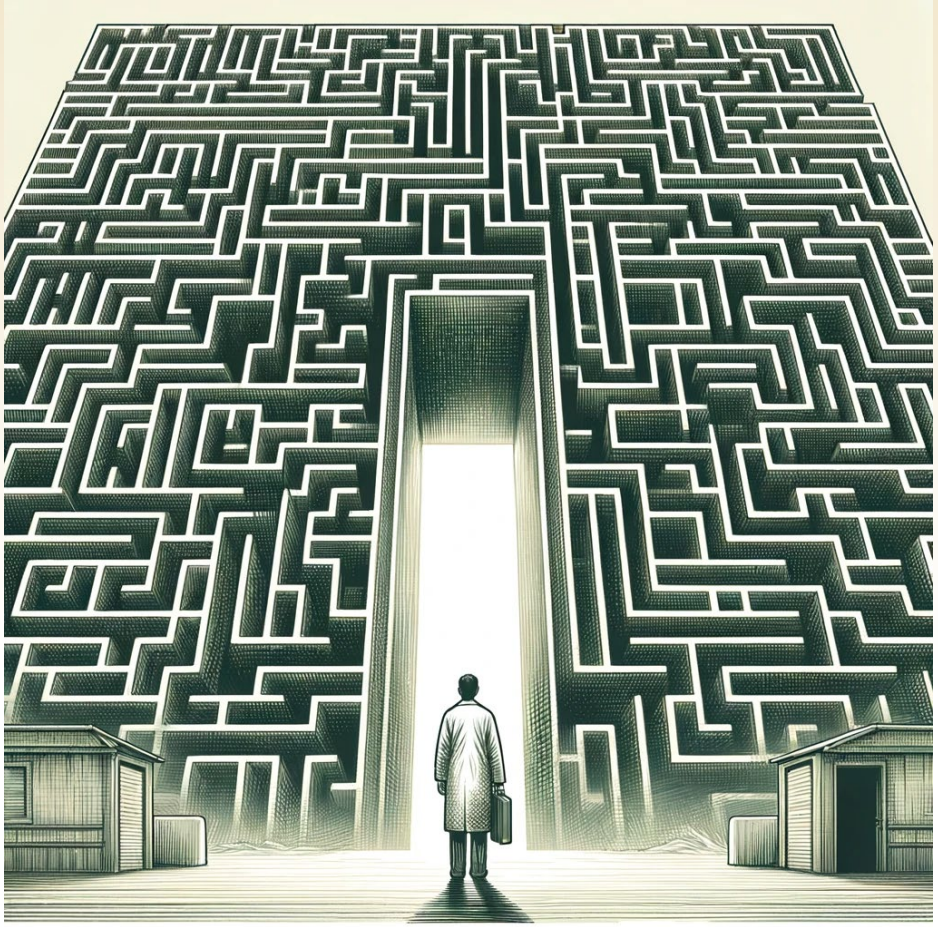


Too much for even one very good doctor to know



How Can a Clinician Know Enough?

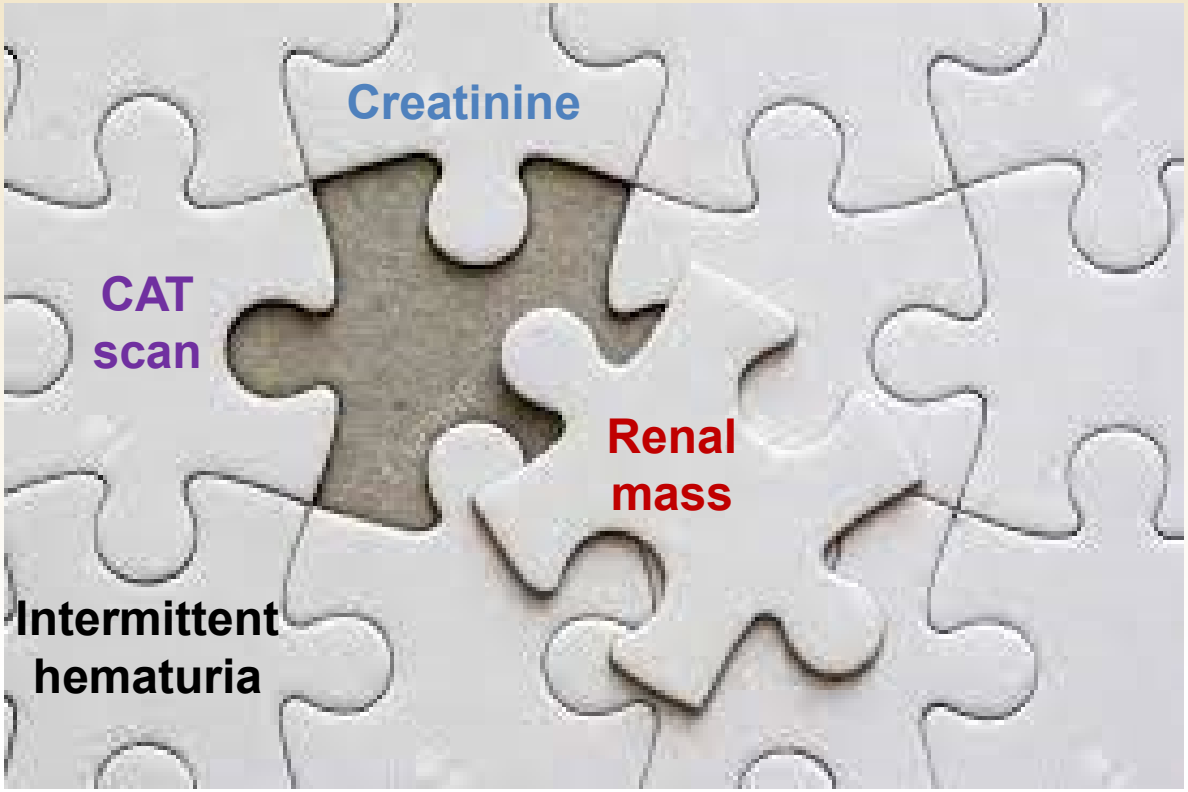
- They are ordering the right non-routine tests?
- They are making the most up-to-date interpretation of the test results for the patient in their current state?



The Diagnostic Center Allows for Easy Access to Experts in All Diagnostic Fields

- Up-to-date interpretation
- Patient-specific
- Automated for fast delivery
- Actionable next step recommendations

Integrative Diagnostics Must Be Implemented - There are Major Barriers to This Challenge



History and physical exam

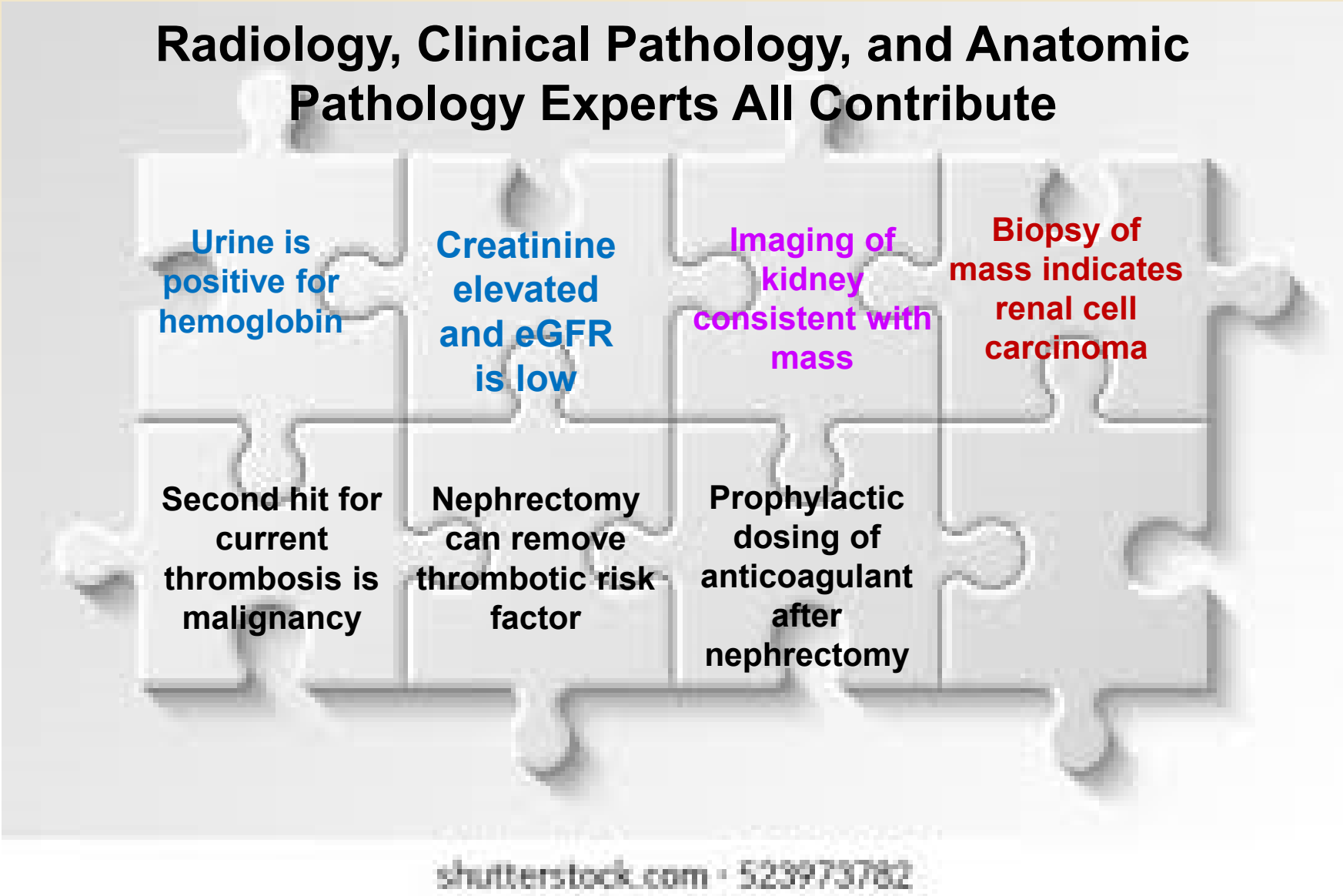
Clinical pathology with genetics

Anatomic pathology

Radiology

Evaluation for Thrombotic Risk to Identify All Contributors to a Thrombotic Event

Radiology, Clinical Pathology, and Anatomic Pathology Experts All Contribute



The recognition of diagnostic error and the assessment of its severity

2014-2015

The largest contributor to preventable death from medical error is

Diagnostic Error

as reported by a committee sponsored by the National Academy of Medicine

Just to show you how little everyone knows about this…..

Why is there no urgency when it is documented by the National Academy of Medicine that there are more than 60,000 preventable deaths in the US annually,

Far more than all the mass shootings combined?

ORIGINAL RESEARCH

Burden of serious harms from diagnostic error in the USA

David E Newman-Toker ,[1,2] Najlla Nassery,[3] Adam C Schaffer,[4,5] Chihwen Winnie Yu-Moe,[5] Gwendolyn D Clemens,[6] Zheyu Wang,[6,7] Yuxin Zhu,[1,6] Ali S. Saber Tehrani,[1] Mehdi Fanai,[1] Ahmed Hassoon,[1,2] Dana Siegal[8,9]

"Across clinical settings (ambulatory clinics, emergency department and inpatient), we estimate that nearly 800 000 Americans die or are permanently disabled by diagnostic error each year, making it the single largest source of serious harms from medical mistakes."

BMJ Quality & Safety 2023; 33 82-85
Published Online First: 04 Oct 2023.
doi: 10.1136/bmjqs-2023-016496

The Concept of Consultation on Clinical Lab Test Selection and Expert-Driven Result Interpretation has always been viewed as needed-

But

Implementation of an effective mechanism to do it has been evasive

The challenges within pathology associated with fixing the problem include:

Fear of Obsolescence

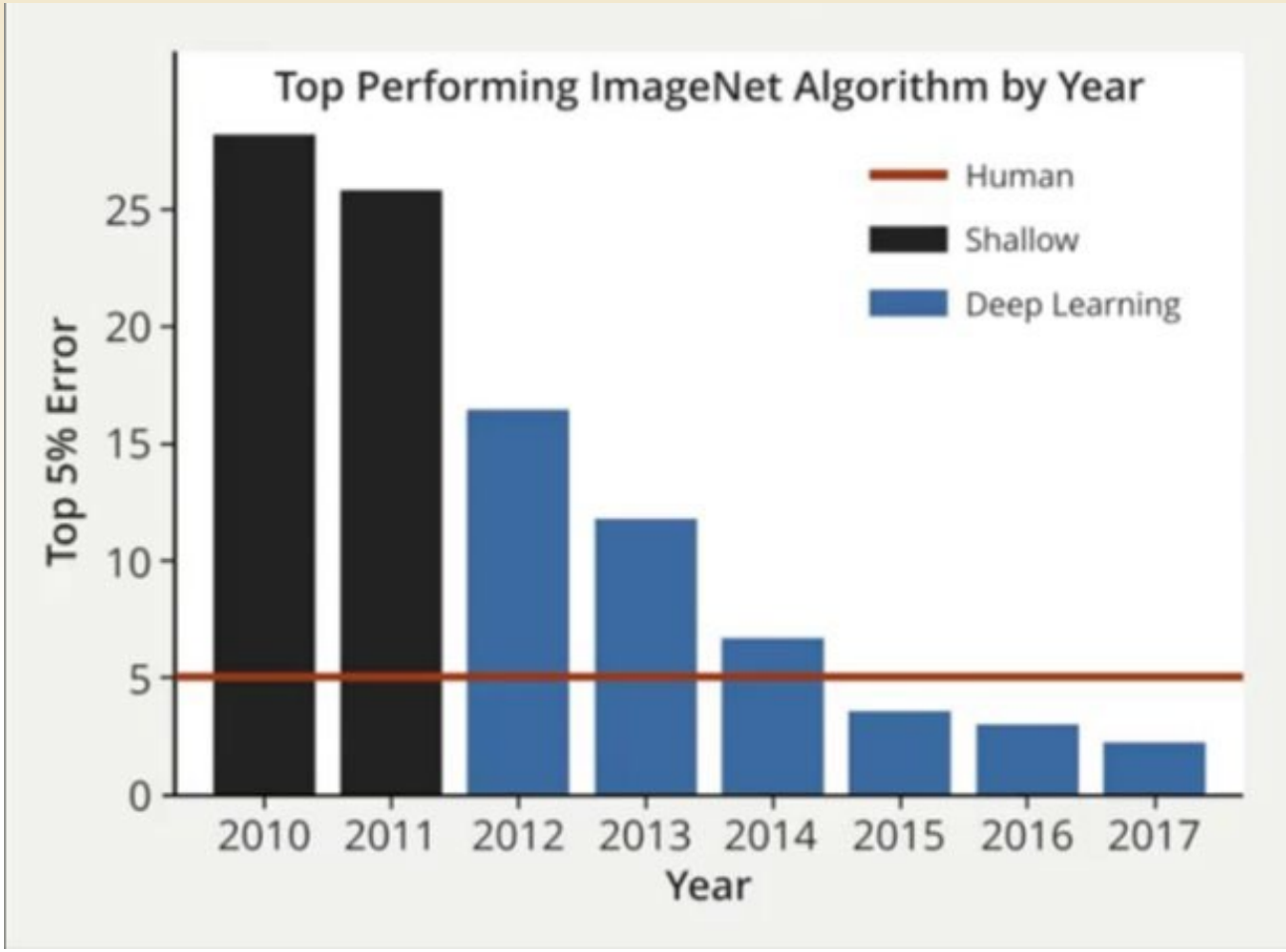
Fear of Income Loss

Fear of Acquisition of Significant New Clinical Responsibilities

The Fear that Artificial Intelligence will Reduce Pathologist Income

Developing Quickly in Radiology and Anatomic Pathology

Diagnostic Algorithms Can Detect Lung Cancer and Classify the Lesions



Deep learning improved the performance of the reading instrument to match and then outperform the pathologist

An empty cockpit? An instrument deciding if your biopsy is malignant?

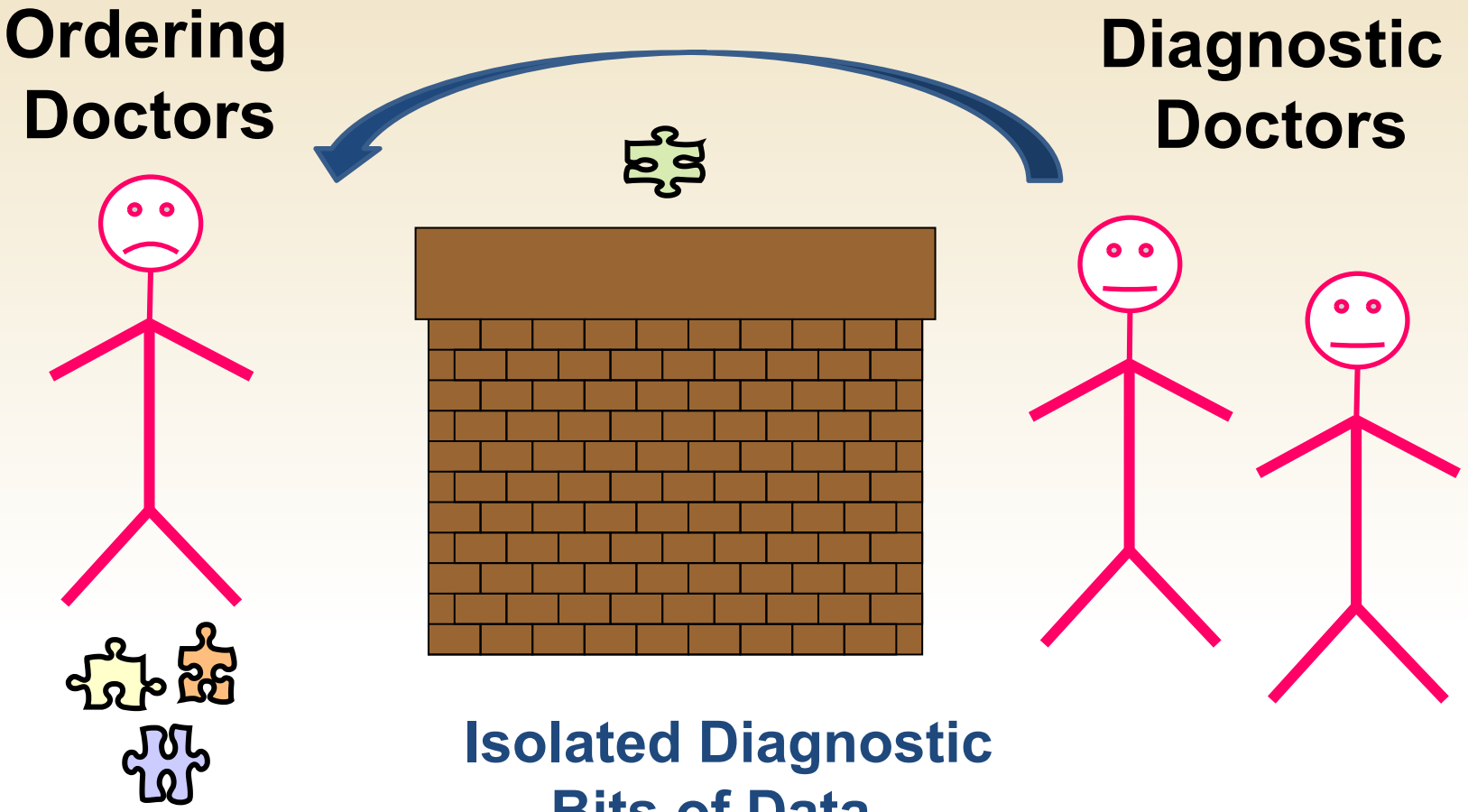
Even if there is a computer system to fly an airplane, it will never be without a pilot

The same is true for a pathologist and a biopsy

THE CONSEQUENCES OF A MISTAKE ARE TOO ENORMOUS

Expert teams to advise doctors on appropriate test selection and correct result interpretation may reduce the value of the local pathologist

Passive Laboratory-Virtually every clinical lab in the United States



Isolated Diagnostic Bits of Data - Assembly by Ordering Physician Minimally Trained in Test Selection and Interpretation

Not choosing pathology – An essay-based survey of first-year clinical residents

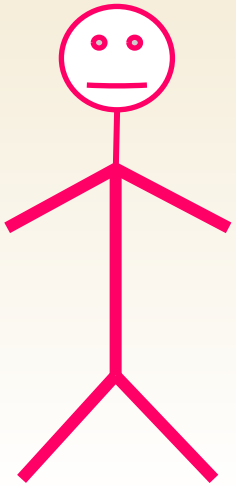
The 11 most common reasons why graduates did not choose pathology as a specialty were identified.

The top reason was a perception that pathology lacks practical application to patient care or offers "no real help" (48.2%).

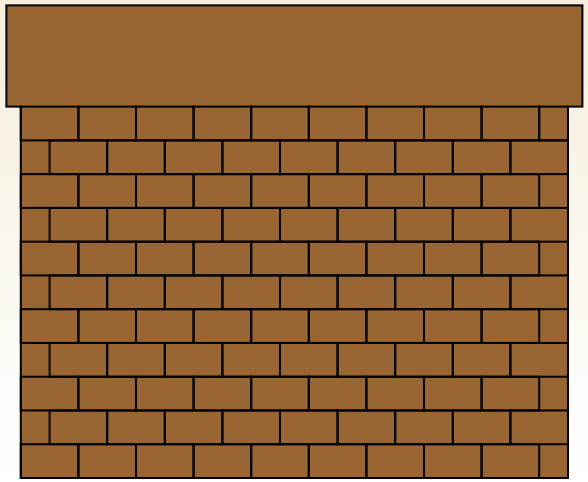
2023; 1*Am J Clin Pathol* 60:593-598

Until recently there was minimal payment for picking up the pieces and establishing a diagnosis

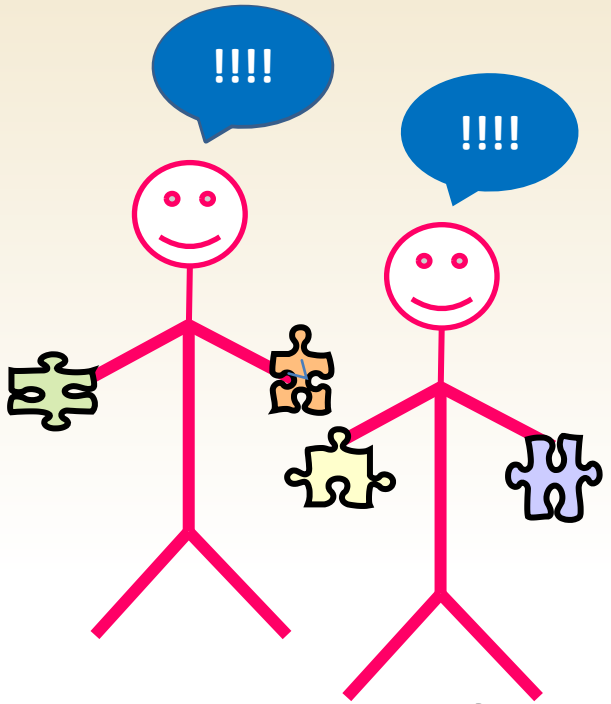
Ordering Doctors



Caring for More Patients While Diagnostic Puzzle is Being Assembled



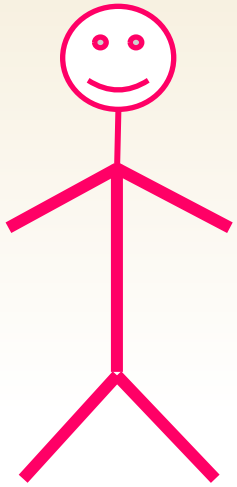
Conferring Diagnostic Doctors



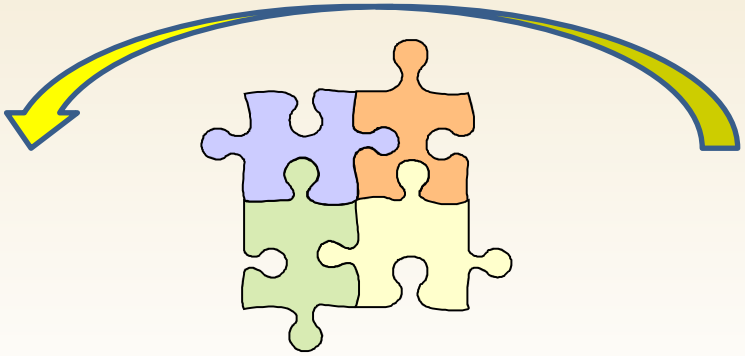
Isolated Diagnostic Bits of Data Being Merged with Clinical Data about the Patient by the Diagnostic Doctors

There was certainly no payment for having a collegial discussion and educating the patient facing physician

Ordering Doctors

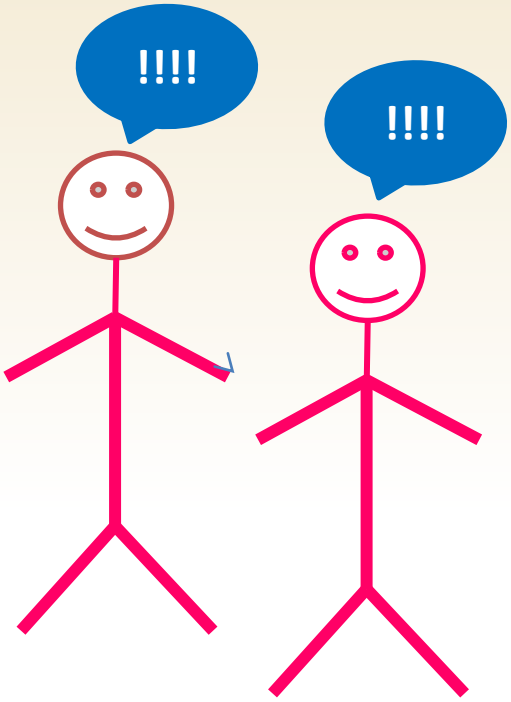


Solved Diagnostic Puzzle



There Is No Wall between the Ordering Doctors and the Diagnostic Doctors

Conferring Diagnostic Doctors



Receives Accurate Diagnosis Quickly as a Completed Puzzle

Original Idea : DMTs in all major institutions
Response : Too much diagnostic medicine to learn with too little financial return

- **Diagnostic Center is the source for all diagnostic evaluations**
- **The Diagnostic Center is paid for its consultation**
- **If a local pathologist is part of the consultation, diagnostic codes should be able to be used for that activity**

JOHN SEALY DIAGNOSTIC CENTER

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Diagnostic Center Team

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The focus of the Diagnostic Center is almost exclusively on

Establishing a Diagnosis

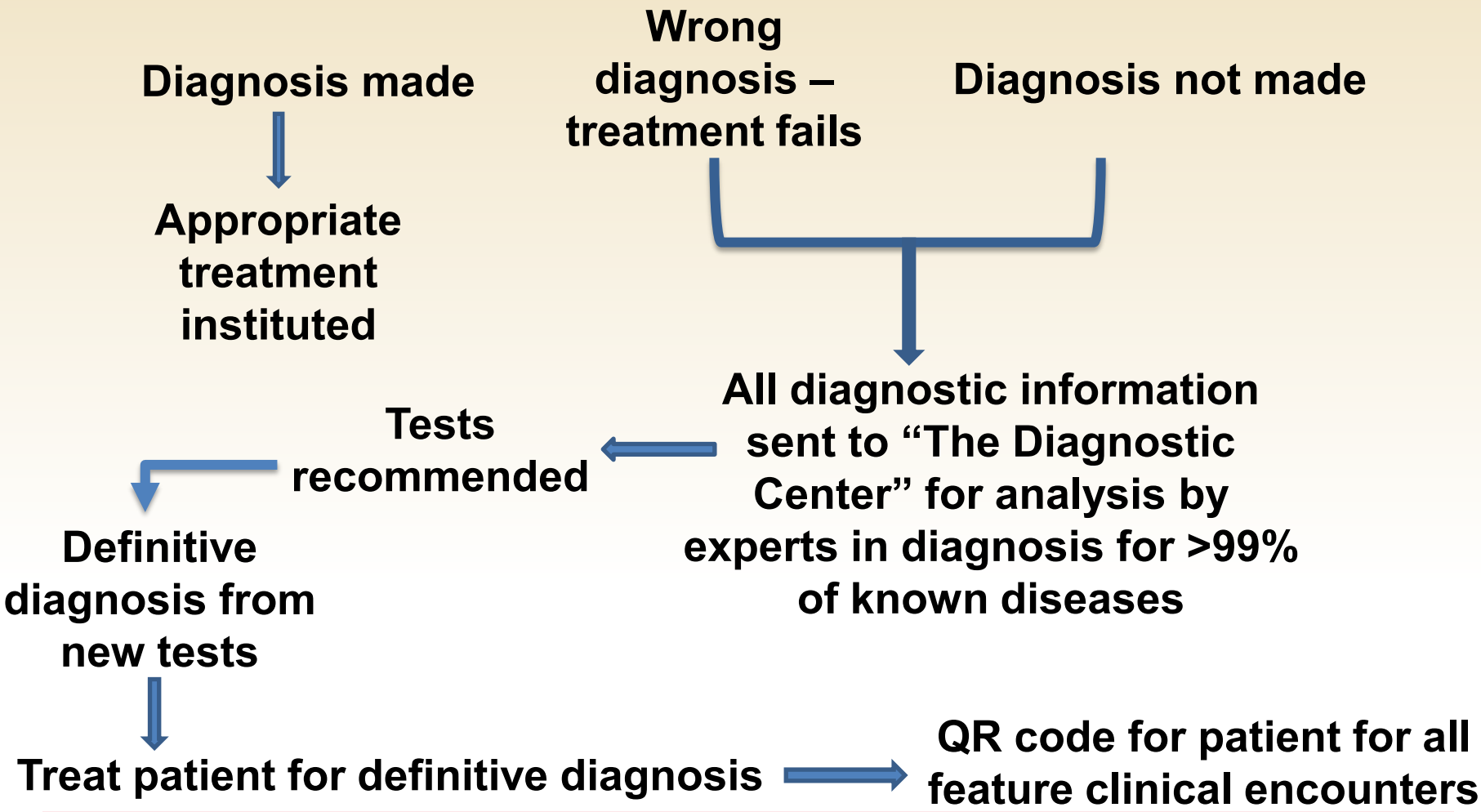
with treatment left to the patient facing provider

There is no plan to compete for laboratory test performance or the patient

Niche laboratory test performance will be offered as an option

This is a unique service in the practice of medicine

How the Diagnostic Center Works



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Attempts to provide a solution

The Diagnosis Identifies the Condition and Permits Effective Treatment

How large is the contribution of the pathologist?

Illness

↓

Diagnosis made with tests

↓

Treat the illness identified by the diagnostic test results

Doing more tests on a small volume of blood does not solve the problem of diagnostic error

Elizabeth Holmes Theranos CEO

Is performance of battery of diagnostic tests from a fingerstick clinically valuable?

How can someone with only a modicum of engineering experience as a student without the collaboration of clinical chemists or pathologists create a testing device to do >100 tests on a drop of blood

and then convince individuals to invest $9.2 billion in the company

The Missing Clinical Service in US Medicine Today :

Leadership in the Diagnostic Evaluation of Patients

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Current Activities to Create a Solution for Millions of Patients Experiencing Diagnostic Mistakes

For Each DMT to Completer >100 Cases per Day

Case Data → Automation to select codes from Holy Book → Holy Book Interpretive comments reviewed and modified as necessary

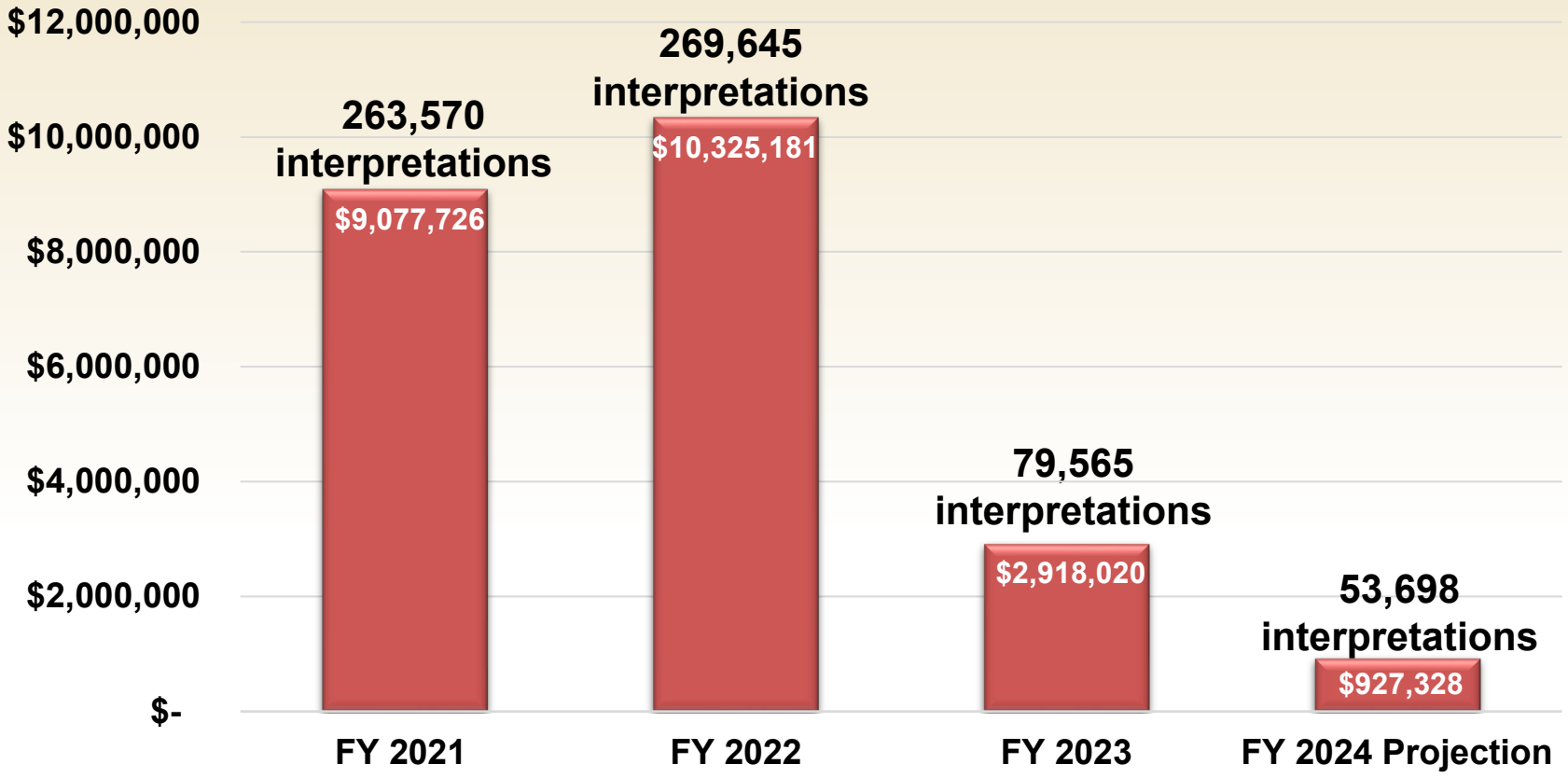
Report sent and case billed

Requirements for All DMTs

- Holy Books of hundreds of interpretive comments
- "Literature Scraping" on a Regular Basis
- Automation from laboratory data to comment selection

COVID Professional Interpretation Revenue

Total professional revenue of $22.3M between October 2020 – August 2023 from 612,780 interpretations



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This experience taught us:

How to build a Holy Book, and keep it up to date with current findings

How to sign out >1000 cases per day

How to bill for the interpretations

How to automate data extraction from Epic and have the system select an appropriate interpretive comment for acceptance or modification by the pathologist

After 31 meetings with the founding group:

A complete holy book on any topic can be produced in a single day

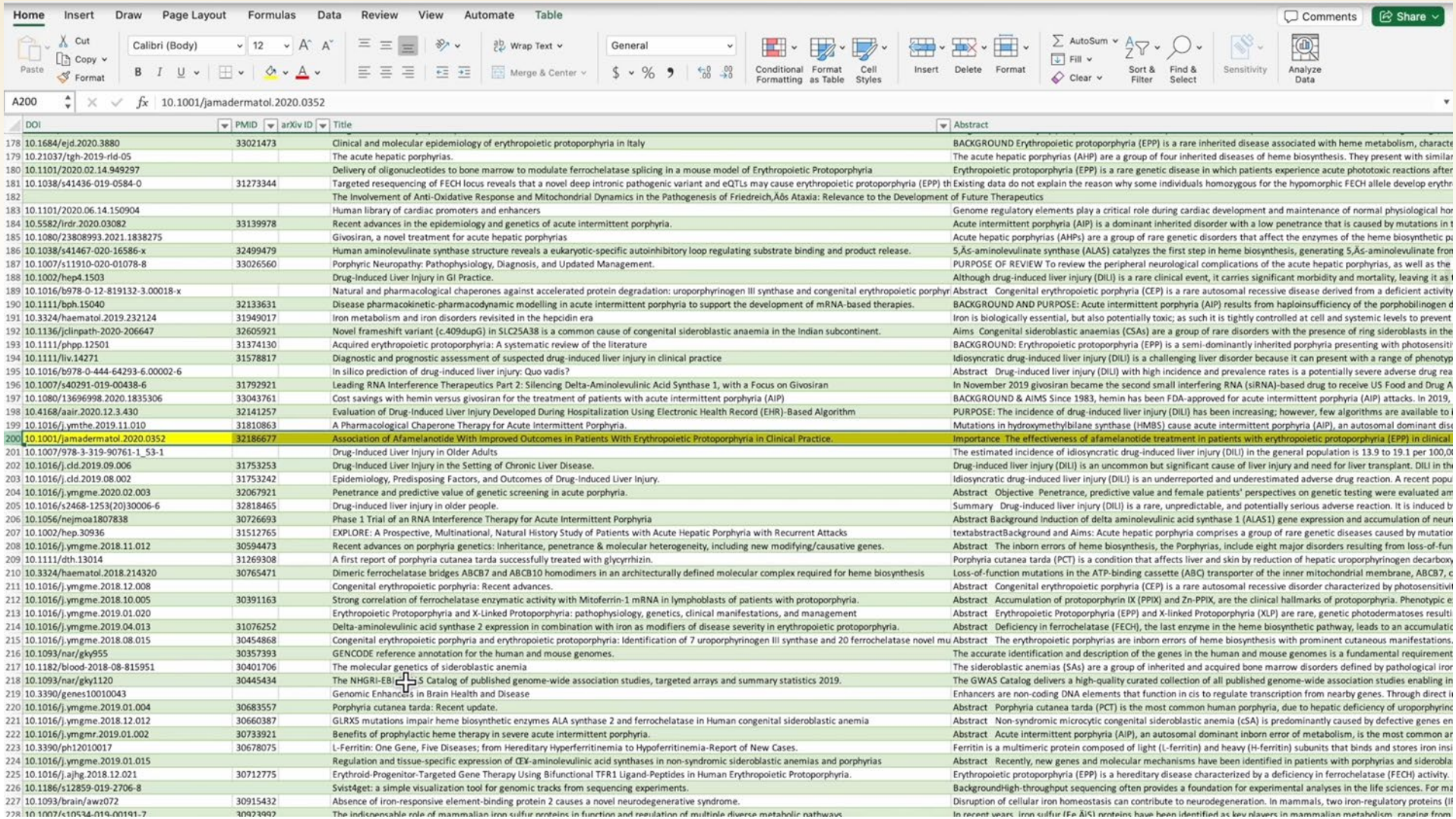
The automation step which extracts data from the medical record can be done in seconds for any topic – and be linked to references

Scraping the literature now is done with artificial intelligence first reading the published articles and directing findings to the pathologist

Maintaining Current Content within Holy Book

"Scraping" the literature

To obtain the latest findings and incorporate them into the existing ones



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A200 10.1001/jamadermatol.2020.0352

	DOI	PMID	arXiv ID	Title	Abstract
178	10.1684/ejd.2020.3880	33021473		Clinical and molecular epidemiology of erythropoietic protoporphyria in Italy	BACKGROUND Erythropoietic protoporphyria (EPP) is a rare inherited disease associated with heme metabolism, characte
179	10.21037/tgh-2019-rld-05			The acute hepatic porphyrias.	The acute hepatic porphyrias (AHP) are a group of four inherited diseases of heme biosynthesis. They present with similar
180	10.1101/2020.02.14.949297			Delivery of oligonucleotides to bone marrow to modulate ferrochelatase splicing in a mouse model of Erythropoietic Protoporphyria	Erythropoietic protoporphyria (EPP) is a rare genetic disease in which patients experience acute phototoxic reactions after
181	10.1038/s41436-019-0584-0	31273344		Targeted resequencing of FECH locus reveals that a novel deep intronic pathogenic variant and eQTLs may cause erythropoietic protoporphyria (EPP) th	Existing data do not explain the reason why some individuals homozygous for the hypomorphic FECH allele develop erythr
182				The Involvement of Anti-Oxidative Response and Mitochondrial Dynamics in the Pathogenesis of Friedreich¿Âõs Ataxia: Relevance to the Development of Future Therapeutics	
183	10.1101/2020.06.14.150904			Human library of cardiac promoters and enhancers	Genome regulatory elements play a critical role during cardiac development and maintenance of normal physiological hor
184	10.5582/irdr.2020.03082	33139978		Recent advances in the epidemiology and genetics of acute intermittent porphyria.	Acute intermittent porphyria (AIP) is a dominant inherited disorder with a low penetrance that is caused by mutations in t
185	10.1080/23808993.2021.1838275			Givosiran, a novel treatment for acute hepatic porphyrias	Acute hepatic porphyrias (AHPs) are a group of rare genetic disorders that affect the enzymes of the heme biosynthetic pa
186	10.1038/s41467-020-16586-x	32499479		Human aminolevulinate synthase structure reveals a eukaryotic-specific autoinhibitory loop regulating substrate binding and product release.	5,Ãs-aminolevulinate synthase (ALAS) catalyzes the first step in heme biosynthesis, generating 5,Ãs-aminolevulinate fron
187	10.1007/s11910-020-01078-8	33026560		Porphyric Neuropathy: Pathophysiology, Diagnosis, and Updated Management.	PURPOSE OF REVIEW To review the peripheral neurological complications of the acute hepatic porphyrias, as well as the
188	10.1002/hep4.1503			Drug-Induced Liver Injury in GI Practice.	Although drug-induced liver injury (DILI) is a rare clinical event, it carries significant morbidity and mortality, leaving it as
189	10.1016/b978-0-12-819132-3.00018-x			Natural and pharmacological chaperones against accelerated protein degradation: uroporphyrinogen III synthase and congenital erythropoietic porphyr	Abstract Congenital erythropoietic porphyria (CEP) is a rare autosomal recessive disease derived from a deficient activity
190	10.1111/bph.15040	32133631		Disease pharmacokinetic-pharmacodynamic modelling in acute intermittent porphyria to support the development of mRNA-based therapies.	BACKGROUND AND PURPOSE: Acute intermittent porphyria (AIP) results from haploinsufficiency of the porphobilinogen d
191	10.3324/haematol.2019.232124	31949017		Iron metabolism and iron disorders revisited in the hepcidin era	Iron is biologically essential, but also potentially toxic; as such it is tightly controlled at cell and systemic levels to prevent
192	10.1136/jclinpath-2020-206647	32605921		Novel frameshift variant (c.409dupG) in SLC25A38 is a common cause of congenital sideroblastic anaemia in the Indian subcontinent.	Aims Congenital sideroblastic anaemias (CSAs) are a group of rare disorders with the presence of ring sideroblasts in the
193	10.1111/phpp.12501	31374130		Acquired erythropoietic protoporphyria: A systematic review of the literature	BACKGROUND: Erythropoietic protoporphyria (EPP) is a semi-dominantly inherited porphyria presenting with photosensiti
194	10.1111/liv.14271	31578817		Diagnostic and prognostic assessment of suspected drug-induced liver injury in clinical practice	Idiosyncratic drug-induced liver injury (DILI) is a challenging liver disorder because it can present with a range of phenotyp
195	10.1016/b978-0-444-64293-6.00002-6			In silico prediction of drug-induced liver injury: Quo vadis?	Abstract Drug-induced liver injury (DILI) with high incidence and prevalence rates is a potentially severe adverse drug rea
196	10.1007/s40291-019-00438-6	31792921		Leading RNA Interference Therapeutics Part 2: Silencing Delta-Aminolevulinic Acid Synthase 1, with a Focus on Givosiran	In November 2019 givosiran became the second small interfering RNA (siRNA)-based drug to receive US Food and Drug A
197	10.1080/13696998.2020.1835306	33043761		Cost savings with hemin versus givosiran for the treatment of patients with acute intermittent porphyria (AIP)	BACKGROUND & AIMS Since 1983, hemin has been FDA-approved for acute intermittent porphyria (AIP) attacks. In 2019,
198	10.4168/aair.2020.12.3.430	32141257		Evaluation of Drug-Induced Liver Injury Developed During Hospitalization Using Electronic Health Record (EHR)-Based Algorithm	PURPOSE: The incidence of drug-induced liver injury (DILI) has been increasing; however, few algorithms are available to
199	10.1016/j.ymthe.2019.11.010	31810863		A Pharmacological Chaperone Therapy for Acute Intermittent Porphyria.	Mutations in hydroxymethylbilane synthase (HMBS) cause acute intermittent porphyria (AIP), an autosomal dominant dise
200	10.1001/jamadermatol.2020.0352	32186677		Association of Afamelanotide With Improved Outcomes in Patients With Erythropoietic Protoporphyria in Clinical Practice.	Importance The effectiveness of afamelanotide treatment in patients with erythropoietic protoporphyria (EPP) in clinical
201	10.1007/978-3-319-90761-1_53-1			Drug-Induced Liver Injury in Older Adults	The estimated incidence of idiosyncratic drug-induced liver injury (DILI) in the general population is 13.9 to 19.1 per 100,0
202	10.1016/j.cld.2019.09.006	31753253		Drug-Induced Liver Injury in the Setting of Chronic Liver Disease.	Drug-induced liver injury (DILI) is an uncommon but significant cause of liver injury and need for liver transplant. DILI in th
203	10.1016/j.cld.2019.08.002	31753242		Epidemiology, Predisposing Factors, and Outcomes of Drug-Induced Liver Injury.	Idiosyncratic drug-induced liver injury (DILI) is an underreported and underestimated adverse drug reaction. A recent popu
204	10.1016/j.ymgme.2020.02.003	32067921		Penetrance and predictive value of genetic screening in acute porphyria.	Abstract Objective Penetrance, predictive value and female patients' perspectives on genetic testing were evaluated am
205	10.1016/s2468-1253(20)30006-6	32818465		Drug-induced liver injury in older people.	Summary Drug-induced liver injury (DILI) is a rare, unpredictable, and potentially serious adverse reaction. It is induced b
206	10.1056/nejmoa1807838	30726693		Phase 1 Trial of an RNA Interference Therapy for Acute Intermittent Porphyria	Abstract Background Induction of delta aminolevulinic acid synthase 1 (ALAS1) gene expression and accumulation of neur
207	10.1002/hep.30936	31512765		EXPLORE: A Prospective, Multinational, Natural History Study of Patients with Acute Hepatic Porphyria with Recurrent Attacks	textabstractBackground and Aims: Acute hepatic porphyria comprises a group of rare genetic diseases caused by mutation
208	10.1016/j.ymgme.2018.11.012	30594473		Recent advances on porphyria genetics: Inheritance, penetrance & molecular heterogeneity, including new modifying/causative genes.	Abstract The inborn errors of heme biosynthesis, the Porphyrias, include eight major disorders resulting from loss-of-fun
209	10.1111/dth.13014	31269308		A first report of porphyria cutanea tarda successfully treated with glycyrrhizin.	Porphyria cutanea tarda (PCT) is a condition that affects liver and skin by reduction of hepatic uroporphyrinogen decarboxy
210	10.3324/haematol.2018.214320	30765471		Dimeric ferrochelatase bridges ABCB7 and ABCB10 homodimers in an architecturally defined molecular complex required for heme biosynthesis	Loss-of-function mutations in the ATP-binding cassette (ABC) transporter of the inner mitochondrial membrane, ABCB7, c
211	10.1016/j.ymgme.2018.12.008			Congenital erythropoietic porphyria: Recent advances.	Abstract Congenital erythropoietic porphyria (CEP) is a rare autosomal recessive disorder characterized by photosensitivit
212	10.1016/j.ymgme.2018.10.005	30391163		Strong correlation of ferrochelatase enzymatic activity with Mitoferrin-1 mRNA in lymphoblasts of patients with protoporphyria.	Abstract Accumulation of protoporphyrin IX (PPIX) and Zn-PPIX, are the clinical hallmarks of protoporphyria. Phenotypic e
213	10.1016/j.ymgme.2019.01.020			Erythropoietic Protoporphyria and X-Linked Protoporphyria: pathophysiology, genetics, clinical manifestations, and management	Abstract Erythropoietic Protoporphyria (EPP) and X-linked Protoporphyria (XLP) are rare, genetic photodermatoses resulti
214	10.1016/j.ymgme.2019.04.013	31076252		Delta-aminolevulinic acid synthase 2 expression in combination with iron as modifiers of disease severity in erythropoietic protoporphyria.	Abstract Deficiency in ferrochelatase (FECH), the last enzyme in the heme biosynthetic pathway, leads to an accumulatio
215	10.1016/j.ymgme.2018.08.015	30454868		Congenital erythropoietic porphyria and erythropoietic protoporphyria: Identification of 7 uroporphyrinogen III synthase and 20 ferrochelatase novel mu	Abstract The erythropoietic porphyrias are inborn errors of heme biosynthesis with prominent cutaneous manifestations.
216	10.1093/nar/gky955	30357393		GENCODE reference annotation for the human and mouse genomes.	The accurate identification and description of the genes in the human and mouse genomes is a fundamental requirement
217	10.1182/blood-2018-08-815951	30401706		The molecular genetics of sideroblastic anemia	The sideroblastic anemias (SAs) are a group of inherited and acquired bone marrow disorders defined by pathological iron
218	10.1093/nar/gky1120	30445434		The NHGRI-EBI GWAS Catalog of published genome-wide association studies, targeted arrays and summary statistics 2019.	The GWAS Catalog delivers a high-quality curated collection of all published genome-wide association studies enabling in
219	10.3390/genes10010043			Genomic Enhancers in Brain Health and Disease	Enhancers are non-coding DNA elements that function in cis to regulate transcription from nearby genes. Through direct i
220	10.1016/j.ymgme.2019.01.004	30683557		Porphyria cutanea tarda: Recent update.	Abstract Porphyria cutanea tarda (PCT) is the most common human porphyria, due to hepatic deficiency of uroporphyrino
221	10.1016/j.ymgme.2018.12.012	30660387		GLRX5 mutations impair heme biosynthetic enzymes ALA synthase 2 and ferrochelatase in Human congenital sideroblastic anemia	Abstract Non-syndromic microcytic congenital sideroblastic anemia (cSA) is predominantly caused by defective genes en
222	10.1016/j.ymgmr.2019.01.002	30733921		Benefits of prophylactic heme therapy in severe acute intermittent porphyria.	Abstract Acute intermittent porphyria (AIP), an autosomal dominant inborn error of metabolism, is the most common ar
223	10.3390/ph12010017	30678075		L-Ferritin: One Gene, Five Diseases; from Hereditary Hyperferritinemia to Hypoferritinemia-Report of New Cases.	Ferritin is a multimeric protein composed of light (L-ferritin) and heavy (H-ferritin) subunits that binds and stores iron insi
224	10.1016/j.ymgme.2019.01.015			Regulation and tissue-specific expression of Œ¥-aminolevulinic acid synthases in non-syndromic sideroblastic anemias and porphyrias	Abstract Recently, new genes and molecular mechanisms have been identified in patients with porphyrias and sideroblas
225	10.1016/j.ajhg.2018.12.021	30712775		Erythroid-Progenitor-Targeted Gene Therapy Using Bifunctional TFR1 Ligand-Peptides in Human Erythropoietic Protoporphyria.	Erythropoietic protoporphyria (EPP) is a hereditary disease characterized by a deficiency in ferrochelatase (FECH) activity.
226	10.1186/s12859-019-2706-8			Svist4get: a simple visualization tool for genomic tracks from sequencing experiments.	BackgroundHigh-throughput sequencing often provides a foundation for experimental analyses in the life sciences. For ma
227	10.1093/brain/awz072	30915432		Absence of iron-responsive element-binding protein 2 causes a novel neurodegenerative syndrome.	Disruption of cellular iron homeostasis can contribute to neurodegeneration. In mammals, two iron-regulatory proteins (IF
228	10.1007/s10534-019-00191-7	30923992		The indispensable role of mammalian iron sulfur proteins in function and regulation of multiple diverse metabolic pathways	In recent years, iron sulfur (Fe ÂíS) proteins have been identified as key players in mammalian metabolism, ranging from

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Selected Expert Teams and Benefits to Patient Outcome and Financial Return

To Be Implemented in the Diagnostic Center

Diagnostic Evaluations For People with No Apparent Illness

Pharmacogenetics

Exome Analysis

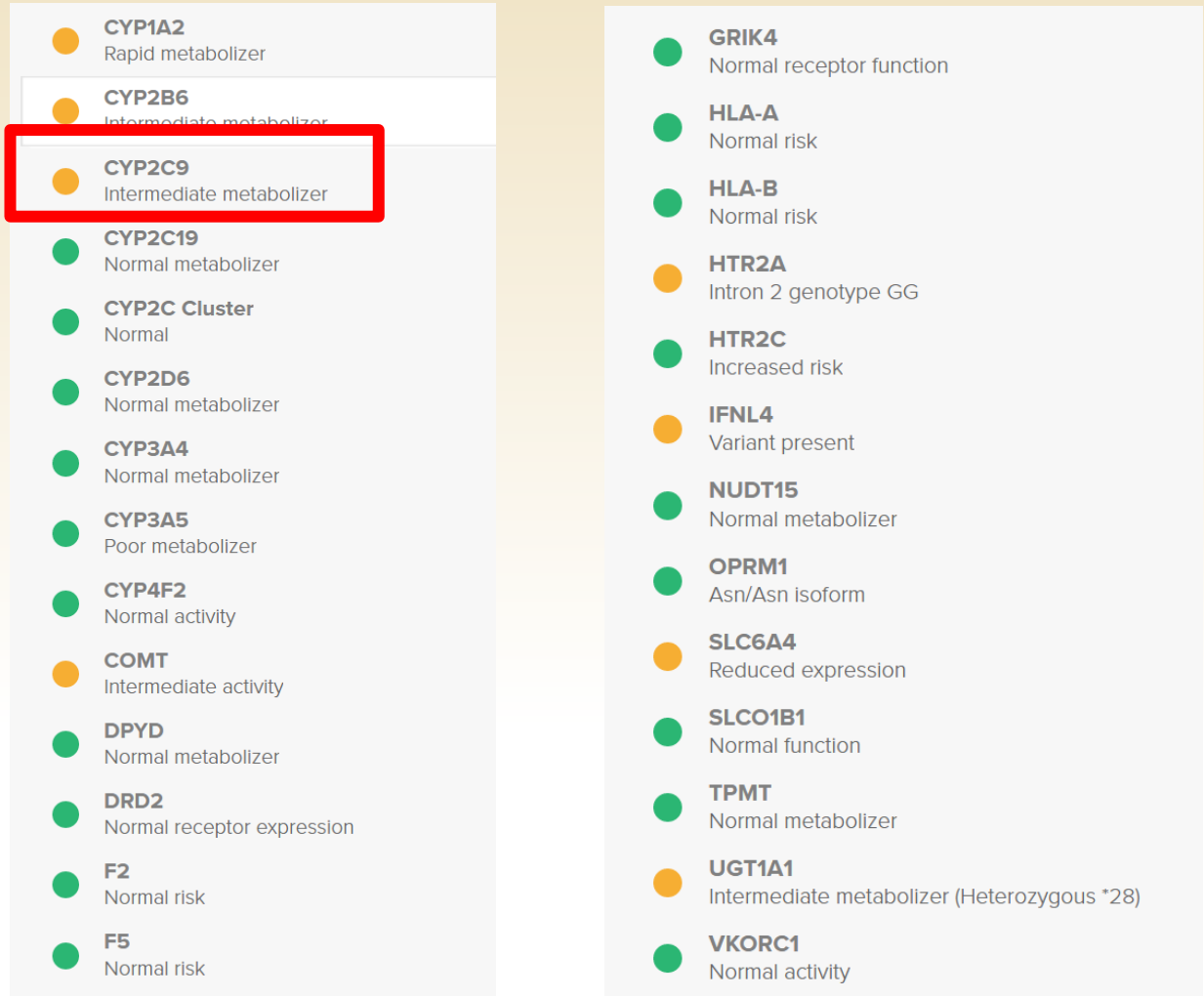
Cancer Screening

Clinical Benefit from the Pharmacogenomics DMT

The benefit of taking the most effective drug is obvious, but it requires an initial investment in a lab test to do so

Making an initial investment in people or equipment involves trust in the person recommending the purchase

Genes Relevant to Pharmacogenomics



Yellow = Altered Metabolism

Green = Normal Metabolism

Focused Report

Medications	Genes with Variants	Metabolizer Status	Recommendations for Prescriber
Atorvastatin (Lipitor)	*SLCO1 B1*	Decreased Function	Prescribe ≤ 40 mg as a starting dose and adjust doses of atorvastatin based on disease-specific guidelines. Prescriber should be aware of possible increased risk of myopathy especially for 40 mg dose. If dose > 40 mg is needed for desired efficacy, consider combination therapy (i.e., atorvastatin plus non-statin guideline directed medical therapy.

Exome Analysis for Single Gene Disorder and Cancer Genetics

- **Available upon validation of PacBio**

- **Can send out testing for special cases at this time**

Exome Analysis for Single Gene Disorder and Cancer Genetics

- If exome analysis shows a high risk for pancreatic cancer, regular abdominal imaging studies to detect an early, surgically curable pancreatic cancer

CAN BE LIFESAVING

Algorithms to Screen for Different Types of Cancer

- An algorithm for testing starts with a test that is neither invasive nor expensive

- If the screening test is positive, the challenge is to find a second level test that is only modestly invasive or expensive

Algorithms to Screen for Different Types of Cancer

- It is understood that the final confirmatory test for cancer is likely to be invasive, expensive, or both

- The goal is to not take individuals who are suspected of having cancer and move them through an evaluation with invasive or expensive tests which may be harmful and not identify cancer

Urine Sample

If Negative, no further evaluation

If Positive, still low likelihood (< 1%) for cancer, but further testing required

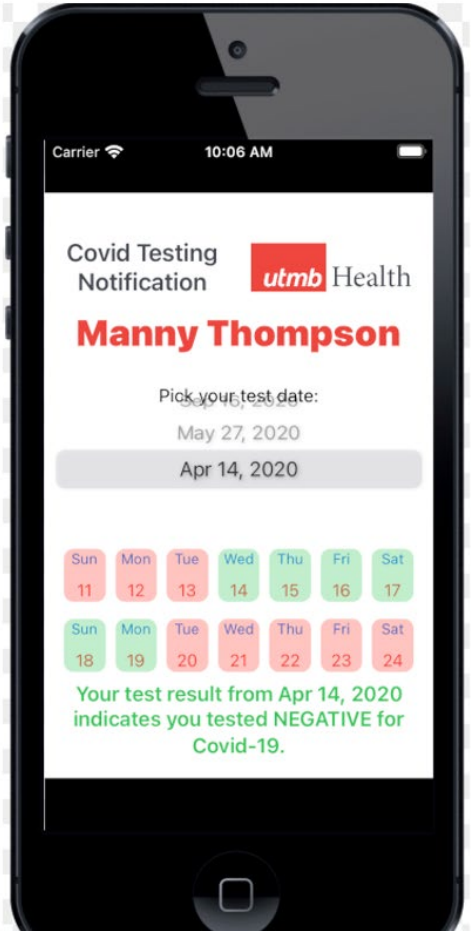
Imaging study of bladder is expensive

Cystoscopy is invasive

Test for Blood in Urine

Identify Less Invasive and Expensive Options

App Sample Concept
Similar to COVID-19 Results Notification



High Intensity and Low Intensity Screening Will be Available

	Age						
	40	42	44	46	48	50	52
Adrenal Gland Cortex Tumors	X					X	
Adrenal Medulla Tumor (pheochromocytoma)		X					X
Bladder Cancer	X	X	X	X	X	X	X

For the Patient with Cancer

A Comprehensive High Sensitivity Cancer Diagnosis DMT

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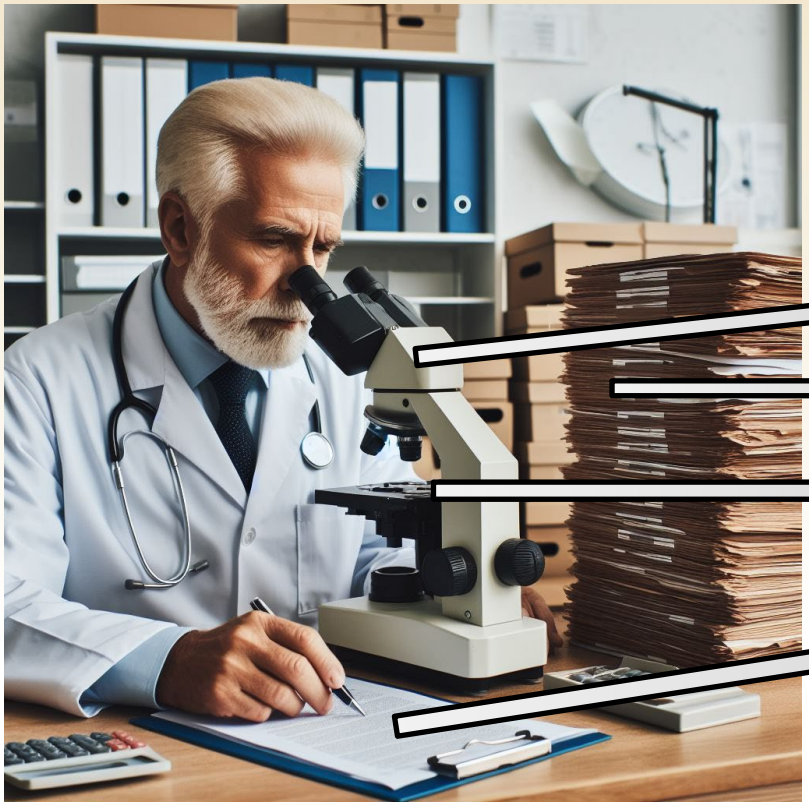
DIGITAL TRANSFORMATION AND ADOPTION OF ARTIFICIAL INTELLIGENCE IN ANATOMIC PATHOLOGY AT UTMB

Traditional Anatomic Pathology



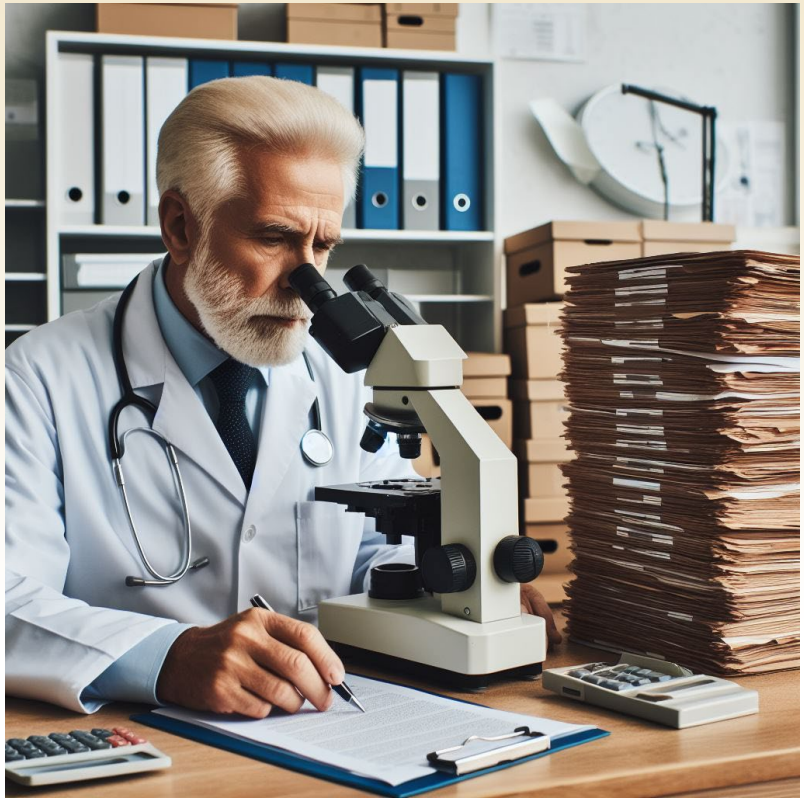
Compound Microscope virtually unchanged since 1830

Paper medical record. Easy to lose. Hard to search

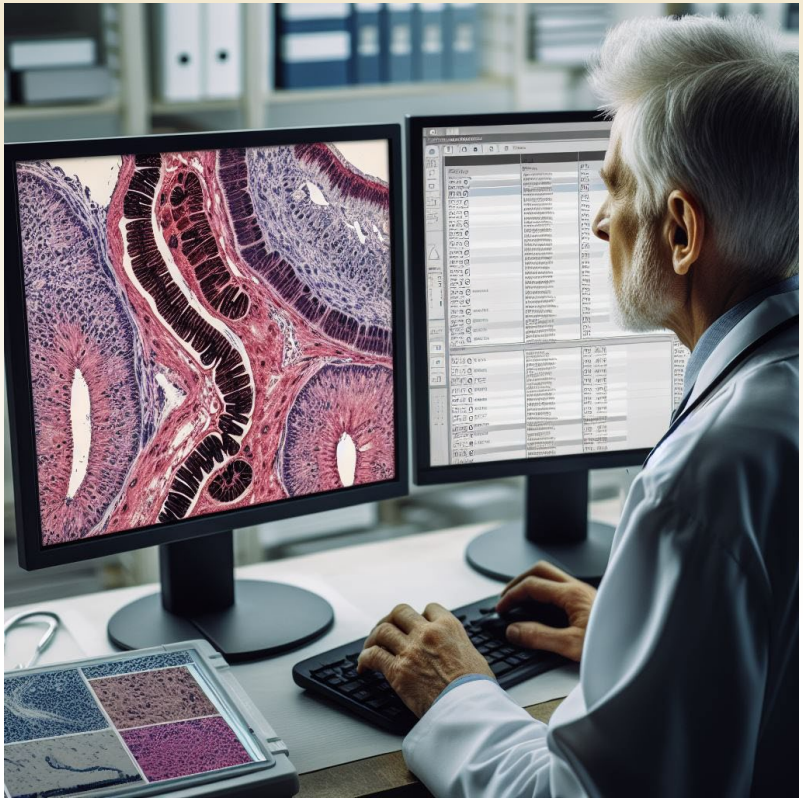
Glass slide. Easy to break. Hard to transport.

Pathologist Report. Subjective. Error prone.

Digital Transformation of Anatomic Pathology



Most other Pathology departments in 2024



UTMB Pathology from 2021 onwards
One of the first all-digital departments in the USA

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Pathologists Working with AI Algorithm get the Best Results

Metric	Pathologist	AI Algorithm	Pathologist with AI
Sensitivity	93%	93%	100%
Specificity	95%	99%	100%
Positive Predictive Value	89%	99%	100%
Negative Predictive Value	97%	97%	100%

Pathologists make mistakes, AI makes mistakes. Together they get it right.

Breast Cancer Genetics: Needed for Prognosis and Selection of Best Therapy

High penetrance genes

- *BRCA1*
- *BRCA2*
- *p53*
- *PTEN*
- *STK11*
- *CDH1*

Medium penetrance genes

- CHK2
- ATM
- RAD51C
- BRIP1
- PALB2

Done by PacBio Revio

PacBio Revio Instrument

Will be used for:

- Pharmacogenomic Sequencing
- Whole Exome and Whole Genome Sequencing
- Single-Cell Genomics
- Gene Editing Research

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Diagnostic Evaluations For People with Clinically Apparent Illness

Cardiometabolic DMT

Classical Hematology

Cancer Screening

Diagnostic Evaluations For People with Clinically Apparent Illness

Autoimmunity

Opioid toxicology

Long Covid and Covid Immunity

Fatty liver of obesity

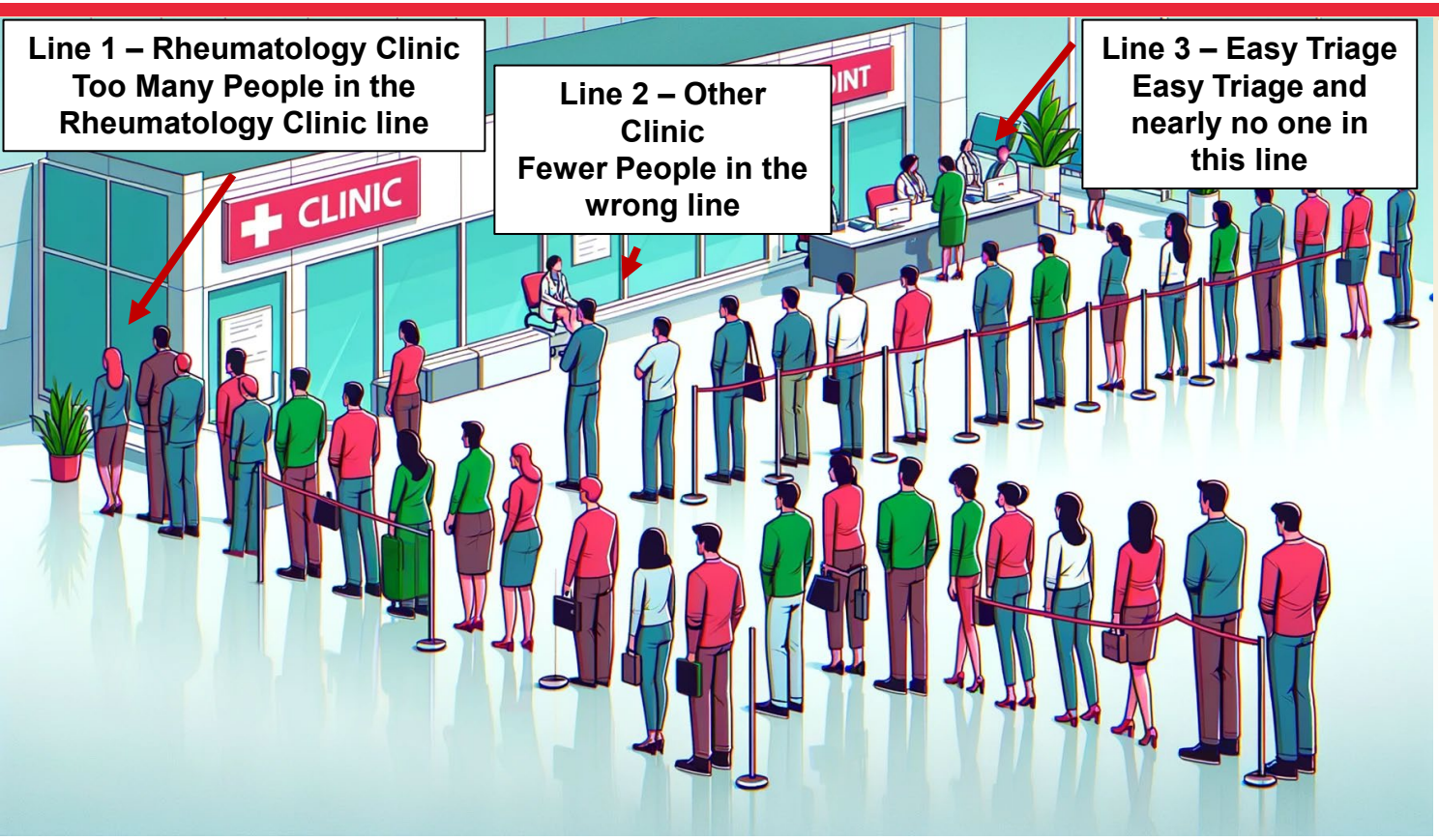
Unexpected benefits of the test recommendations and result interpretations provided by pathologists in the Diagnostic Center

Reduction of Physician "Pajama Time" : Interpretation of Routine Tests with Abnormal Results

- CBC shows MCV with 1 percentage point high
- Chemistry panel shows ALT and AST with minor elevation

Patient wants an email or phone call with her physician about both

Improve Patient Access By Seeing the Right Ones



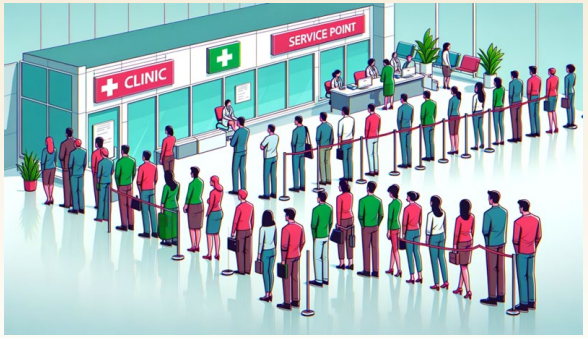
Clothes Key:
Red Clothes – High Suspicion for Rheumatologic Disease

Blue and White Clothes – Intermediate Suspicion for Rheumatologic Disease BUT most likely positive for SOME Disease

Green Clothes – Low suspicion of Disease

Survey of Rheumatology

- **By our estimation**
  - **33.7% of patients could be Delayed or Triaged completely (Green Clothes)**
  - **17.8% of patients would have additional tests performed prior to visit making it easier for Rheumatology (White/Blue Clothes)**
  - **Leaving 48.5% of patients with high suspicion of disease clear to be seen in the Clinic (Red Clothes)**



There are at least 50 DMTs in line

They can be organized by

Disease group: Coagulation

Presenting sign/symptom: Bleeding

Abnormal laboratory test result: Prolonged PTT

A “Trigger” sign or symptom or lab test result will ideally create an option for a Diagnostic Center consult

Potential Clients for the Diagnostic Center

- Health Care Enterprises
- Academic Medical Centers
- Community Hospitals

Potential Clients for the Diagnostic Center

- Sick patients
- Healthy patients for Pharmacogenomics and Exome Analysis
- International clients – physicians/patients
- Concierge/VIP patients

When Can Individual DMTs within the Diagnostic Center Be Fully Operational?

Only when the potential demand for hundreds of cases per day can be met for every diagnostic area

Waiting for the New Iphone: Are There Enough?

Why Did it Take 30 Years?

Original idea : 1984
First implementation for coagulation only : 1995
First major national presentations of concept and service : 1997-98
Creation of Diagnostic Management Team name : 2010
Three National meetings on the DMT : 2017-2019
Implementation of 5 new DMTs, including one for alleged child abuse cases : 2014-2024

And then the pandemic occurred, and a clinical need and a new opportunity appeared that launched the DMT with much greater capacity

“Recent” Technical Advances in Construction of the Eiffel Tower Were Absolutely Required for its Construction

The tallest structure of its time could only have been built because of technical advances developed within 20 years of its construction – which was just over 2 years from January 28, 1887 to March 15, 1889

With less advanced processes, it might have been limited to a height of a few stories and required much more than 2 years to build.

The “Recent” Technical Advances in Construction of the Eiffel Tower Which Were Absolutely Required for its Construction

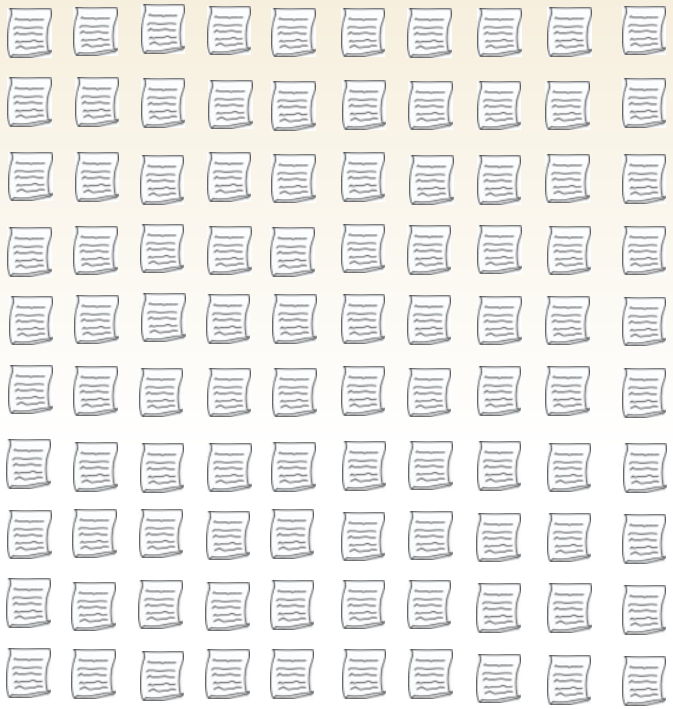
- Iron manufacturing techniques enabled the production of high-quality wrought iron
- Newly advanced calculations in structural engineering permitted optimized lattice structure with necessary strength and flexibility
- Pneumatic riveting available to assemble the towers thousands of elements
- And at least 10 more…

Nearly 30 Years Passed Before the Technical Capabilities Arose to Permit Widespread Interpretation of All Diagnostic Results by Experts in ONE site

10 laboratory interpretations/day prepared manually

- **Vectorization to allow searching of Epic and match it with one of many written comments**
- **Artificial intelligence using generative language models to assemble correct content of interpretive comments**
- **Vector Based Searching to create continuous review of all published literature related to a set of narrative interpretations**

500 interpretations/day prepared with new technology in the same amount of time



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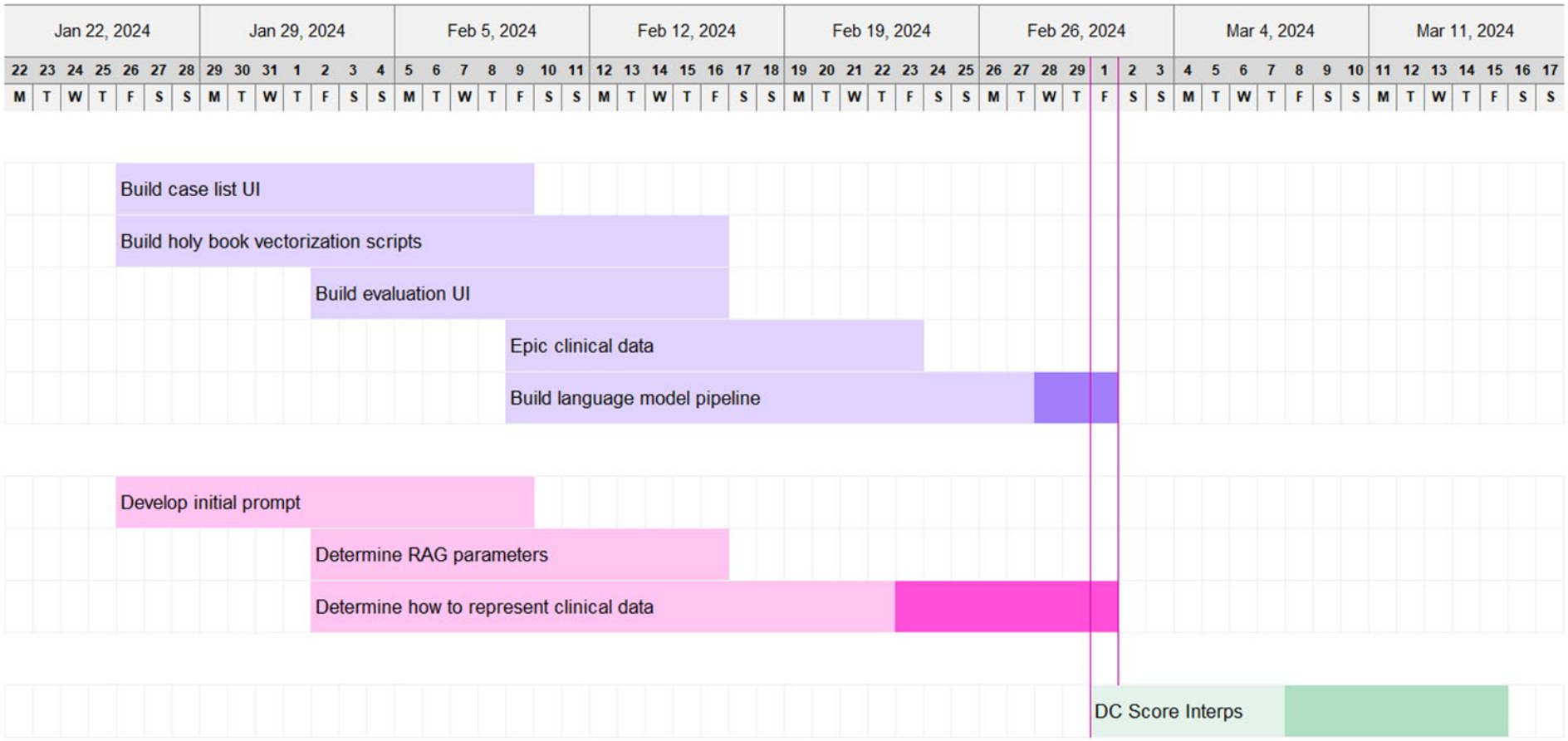
Limitations of the Manual Approach

- **Case volume too low to support a full salary**
- **Content knowledge required of expert is substantial**
- **No expectation of consultative clinical activity – only technical activity**

Grant from Sealy & Smith Foundation

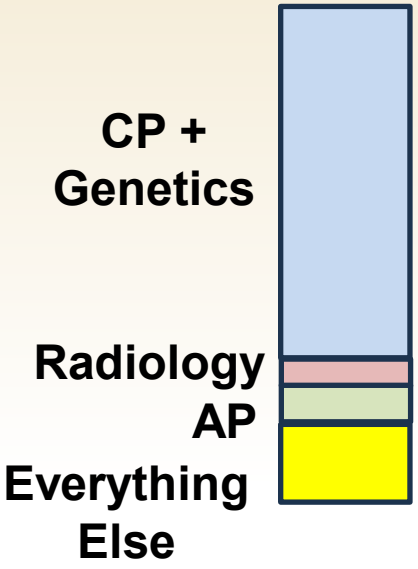
- 9 million dollars over 3 years
- Hiring pathologists and non-pathologists in other roles
- If revenue generation occurs, more pathologists and staff can be hired

SmartSheets – Toxicology example

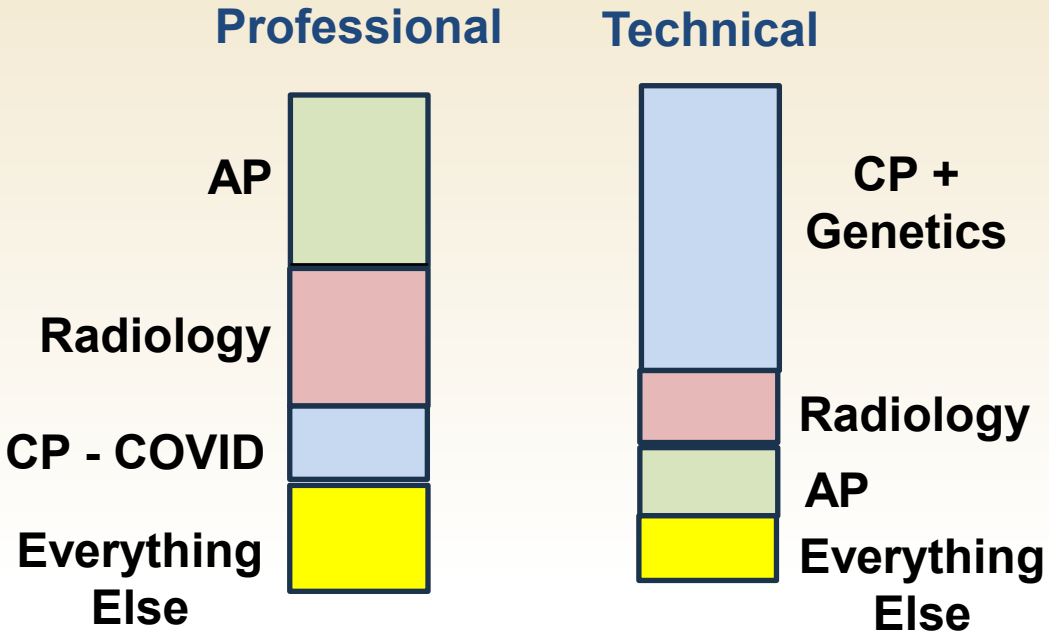


Approximations for UTMB

Number of Different Diagnostic Tests



Revenue from Diagnostic Testing



Strategic Effort to Build a Clinical Service Providing Integrated Diagnostics: Pathology Department

Michael Laposata, M.D., Ph.D.

Professor and Chairman, Department of Pathology

Director, John Sealy Diagnostic Center

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Peter McCaffrey, M.D.

Director of Artificial Intelligence for UTMB

Director, Division of Bioinformatics & Artificial Intelligence

Co-Director, Center for Single Cell Genomics

Medical Director, Laboratory Information Systems

Assistant Professor, Department of Pathology

Assistant Professor, Department of Radiology

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Christopher Zahner, M.D.

Director, Division of Clinical Pathology

Medical Director, Clear Lake, League City, & Angleton Danbury Campus Hospitals

Medical Director, Coagulation, & Point of Care Testing

Assistant Professor, Department of Pathology

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Harsh Thaker, M.D. Ph.D.

Vice Chair, Anatomic Pathology

Professor, Department of Pathology

utmb Health

Juan David Garcia, MBA MLS

Clinical Enterprise Director, Laboratory Services

Director of Operations, John Sealy Diagnostic Center

utmb Health

Bradley Grant, MD, JD

Pharmacogenomics & Molecular Genetics Specialist, John Sealy Diagnostic Center

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Heather Stevenson-Lerner, M.D., Ph.D.

Director of Transplantation Pathology

Professor, Department of Pathology

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Norma Hernandez, MBA

Administrator, UTMB Academic Enterprise

Director of Finance, John Sealy Diagnostic Center

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Amin Mohammad, Ph.D.

Clinical Consultant for the John Sealy Diagnostic Center from Baylor Scott & White

Professor, Pathology

utmb Health

Melanie Connolly, MS

Medical Illustrator & Animator, Department of Surgery

Director of Marketing, John Sealy Diagnostic Center

utmb Health

Christopher Welch, MBA, CBCS

Sr. Finance Manager, John Sealy Diagnostic Center

utmb Health

Carly Goetschius

Program Manager, John Sealy Diagnostic Center

utmb Health

Stephanie Kubachka, MHA, MBA, MLS(ASCP)CM

Manager, Laboratory Services

Project Manager, John Sealy Diagnostic Center

utmb Health

Gladson John

Software Systems Specialist II, John Sealy Diagnostic Center

utmb Health

Victor Luciano

Network Support Specialist, Pathology Administration

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Links to Promotional Videos

General Overview - John Sealy Diagnostic Center.mov
- Dr. Michael Laposata

Intergrating AI.mov – Dr. Peter McCaffrey

DMT Improves Diagnosis Time.mp4 – Dr. Chris Zahner

Dr. Grant Personalized Medicine - Pharmacogenomics.mp4 – Dr. Brad Grant

Digital Transformation and Adoption of Artificial Intelligence in Anatomic Pathology at UTMB.pptx – Dr. Harsh Thaker