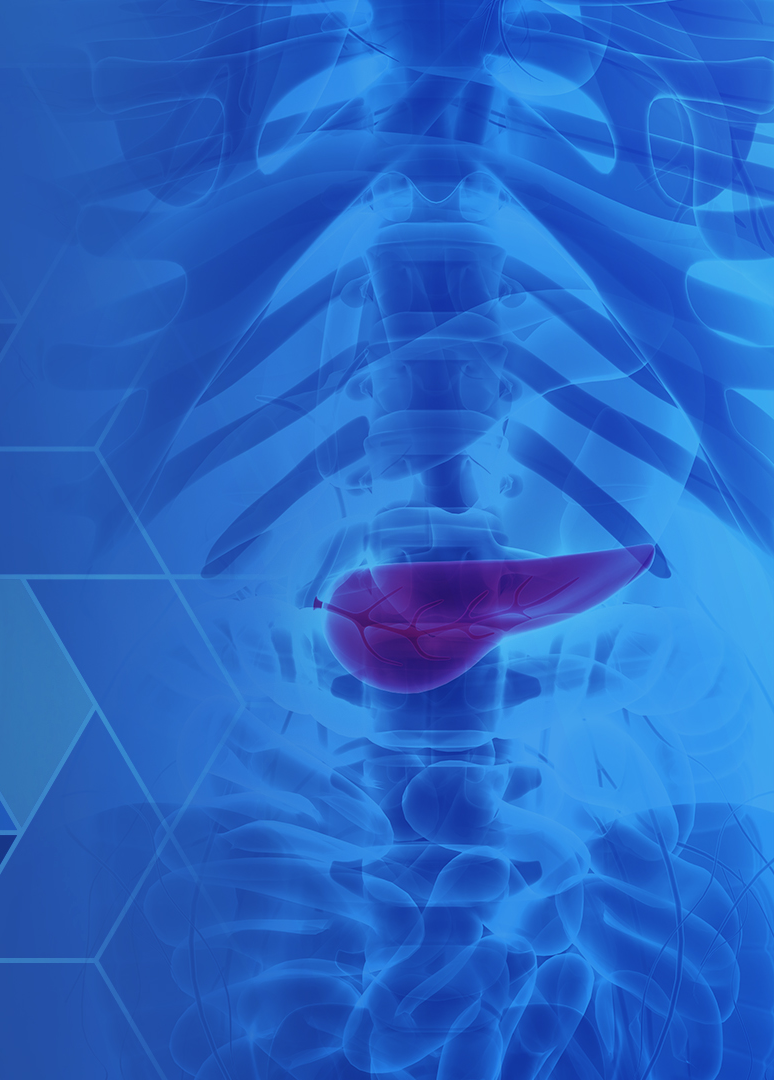
2018 CAPER

Collaborative Alliance for Pancreatic Education and Research

PANCREAS ACADEMY



Rehoboth McKinley Christian Health Care Services

CAPER Collaborative Alliance for Pancreatic Education and Research

Jointly provided by the New Mexico Medical Society (NMMS) through the joint providership of Rehoboth McKinley Christian Health Care Services (RMCHCS) and the Collaborative Alliance for Pancreatic Education and Research.

2018 CAPER Collaborative Alliance for Pancreatic Education and Research
PANCREAS ACADEMY

Precision Medicine in Pancreatic Disease: Where are we now and where are we going

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Outline

- Traditional Medicine
- Precision Medicine
- Challenges and Solutions

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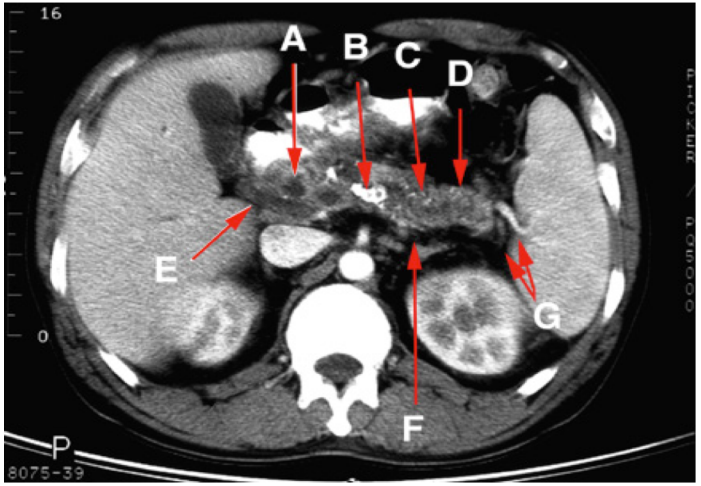
THE PROBLEM

What is Chronic Pancreatitis?

- **Chronic Pancreatitis Syndrome**:
  - **Pancreatic inflammation**
    - Scarring (80%)
    - Maldigestion (40%)
    - Diabetes mellitus (35%)
    - Pain (70% - 5 types)
    - Pancreatic cancer (15%)



- *Diagnosis and Treatment*
  - Diagnosis: requires **demonstration of irreversible damage**
  - Methods: *repeated* CT, MRI, ERCP and/or EUS
  - Treatment: *symptomatic*, pain treatments, PERT, insulin
- ***Summary*: a hopeless, irreversible condition that is expensive to diagnose and treat.**

*Whitcomb DC, *Nature Reviews: G&H*, 2012

Chronic Pancreatitis: 1995
A review of 100 years of research

The New England Journal of Medicine

Medical Progress: Chronic Pancreatitis.

Volume 332(22) 1 Jun 1995 pp 1482-1490

Michael L Steer, Irving Waxman, Steven Freedman

"chronic pancreatitis remains an enigmatic process of uncertain pathogenesis, unpredictable clinical course, and unclear treatment"

Challenge: "Best Practice" is *not good enough!*

Definition: "Chronic pancreatitis is a continuing *inflammatory disease* of the pancreas, characterized by *irreversible morphological change*, and *typically* causing pain and/or permanent loss of function" ("Cambridge Classification" 1984*)

- Inflammation develops – but in whom and why?
- Irreversible morphologic changes ~5 years *after* symptom onset
- "Typical" features known – but with great variability (pain ≠ fibrosis)

Observations:

- The actual "disease" is not defined, but rather an end-stage syndrome
- Pain drives interventions (mostly endoscopic and surgical)
- Early chronic pancreatitis *cannot be diagnosed*
- Therapy is reactive (pain) or supportive (EPI, DM) but *not preventive*
- Little can be done to change the natural history
- *Many* different genetic and environmental factors are "associated" with CP but do not cause CP in most cases (e.g alcohol, smoking)

* Sarner M, Cotton PB. Classification of pancreatitis. Gut. 1984;25(7):756-9. PMID:6735257

Biomedical History

20th Century Medical Paradigm

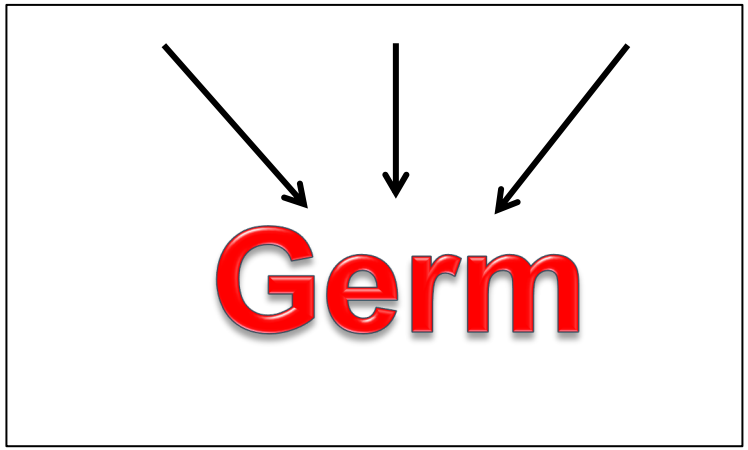
- Based on the "**Germ theory**" of disease
  - One agent → Complex syndrome
- Based on the "**Scientific Method**" of Koch
  - Complex syndrome → one factor
- Based on **clinicopathologic** disease definitions
  - Syndrome, pathology-based (e.g. ICD codes)
- <u>Results</u>:
  - Progress in infectious diseases and simple genetics
  - Poor progress in complex* disorders
  - Little guidance for managing complex disorders

* **Complex disorders**: two or more factors are required. Can be gene x environment, gene x gene, etc. Individual factors may not be *necessary* nor *sufficient* to cause disease.

Germ Theory: Success & Failure

Expected

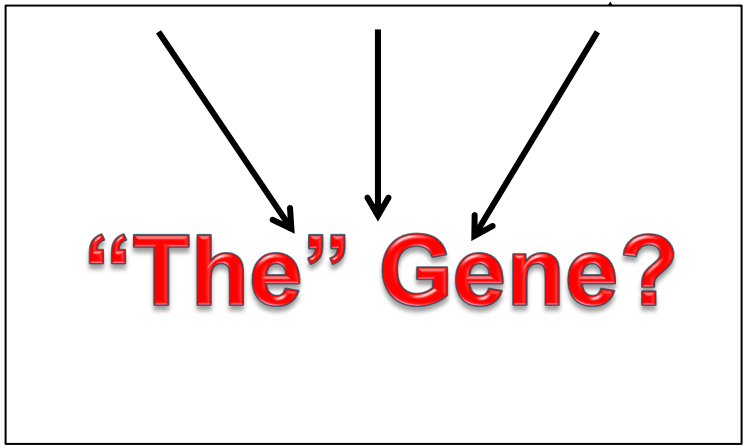
Sx | Inflammation | Pain | Organ dysfunction



Germ Theory:
symptom complex predicts single etiology

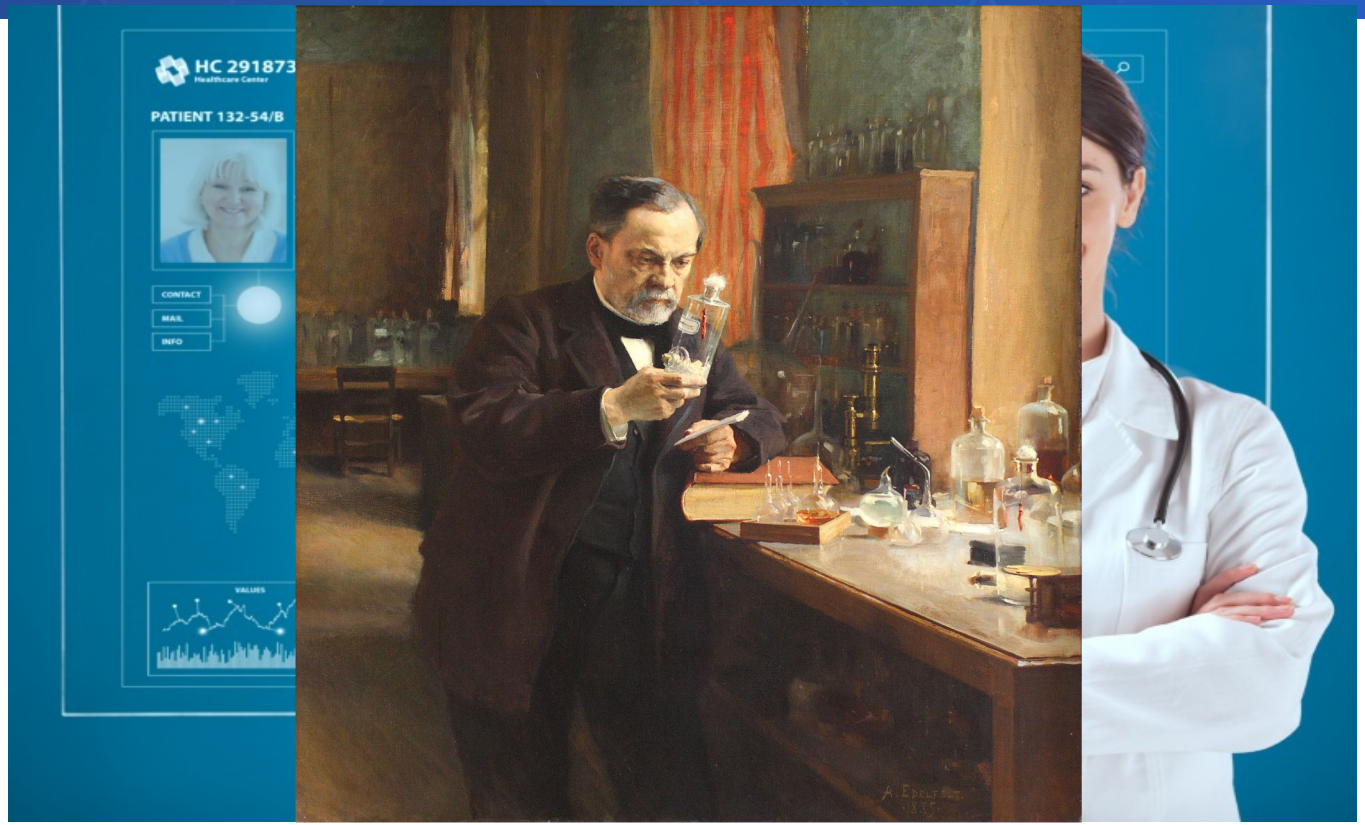
Observed (if no “germ”)

Sx | Inflammation | Pain | Organ dysfunction



Germ Theory:
A *Paradigm Failure*!

A New Paradigm is Needed!



Louis Pasteur in his laboratory

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PERSONALIZED MEDICINE

Personalized Medicine

When is a new paradigm needed?

- **Personalized/Precision/Individualized Medicine**
  - Needed when a "syndrome" is complex
    - Multiple etiologies → same "pathology"
    - Same pathology → multiple outcomes
    - Treatment effects → unpredictable (**NNT >1**)
  - Needed for **Complex & Functional** disorders; [Cancer]
    - Focus on **mechanism** rather than *associations* (RCT)
    - Relies on **modeling** and **simulation**, not *epidemiology.*
    - Guidance for **individuals** rather than *populations*.
  - Requires a **New framework** for new technologies
    - Progressive, mixed disease model [*not* data-driven models from populations]
    - Analysis of multiple factors interacting in **ONE** person
    - Predicts *different* outcomes with changes in key variables (e.g. Rx)
  - **Pancreas is a perfect organ to start modeling**:
    - Three cell types (acinar, duct, islet)
    - Each does ONE primary thing
    - The molecular mechanisms are KNOWN
    - The environmental effects are minimal (except smoking and alcohol)

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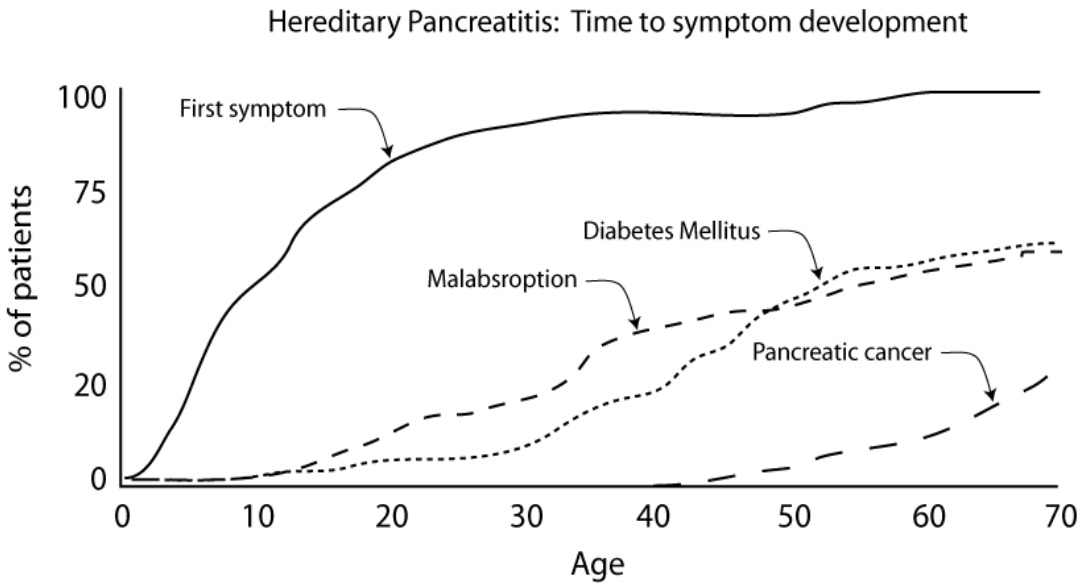
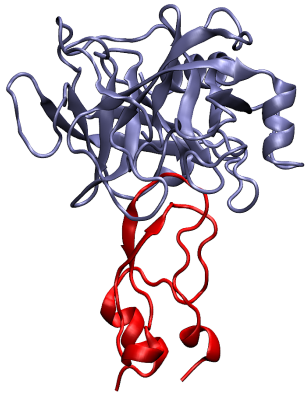
GENETICS: PRSS1, CFTR, CEL, OTHERS

Hereditary Pancreatitis (*PRSS1*)

- **Acute Pancreatitis** in 80% with the *PRSS1* mutation
- **Chronic Pancreatitis** in 50% with acute pancreatitis
- **Pancreatic Cancer** in **~15%** with chronic pancreatitis.



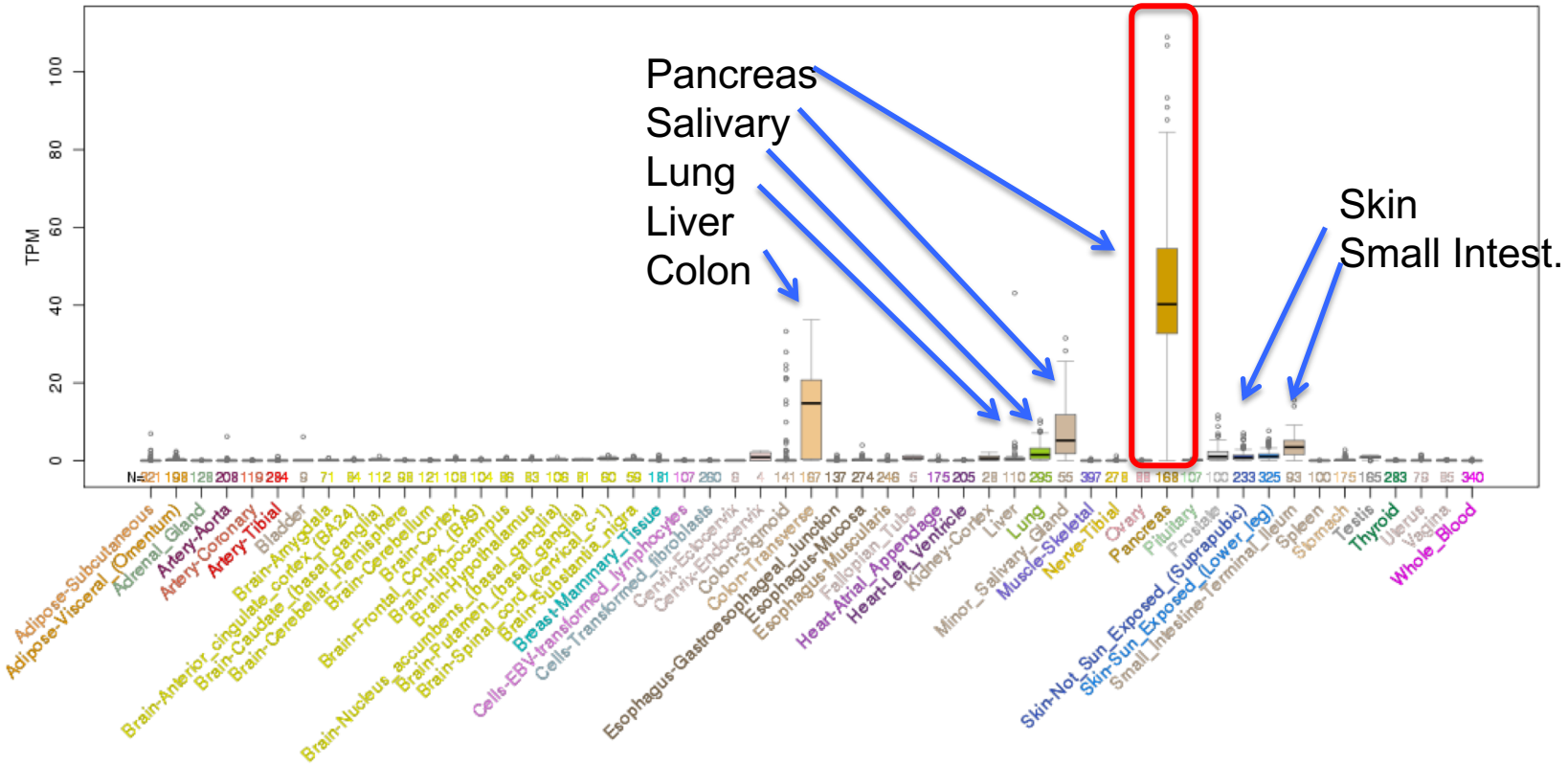
Howes et al. Clin Gastroenterol Hepatol. 2004;2(3):252-61



PRSS1 & *SPINK1*

CFTR Transcritpt Expression

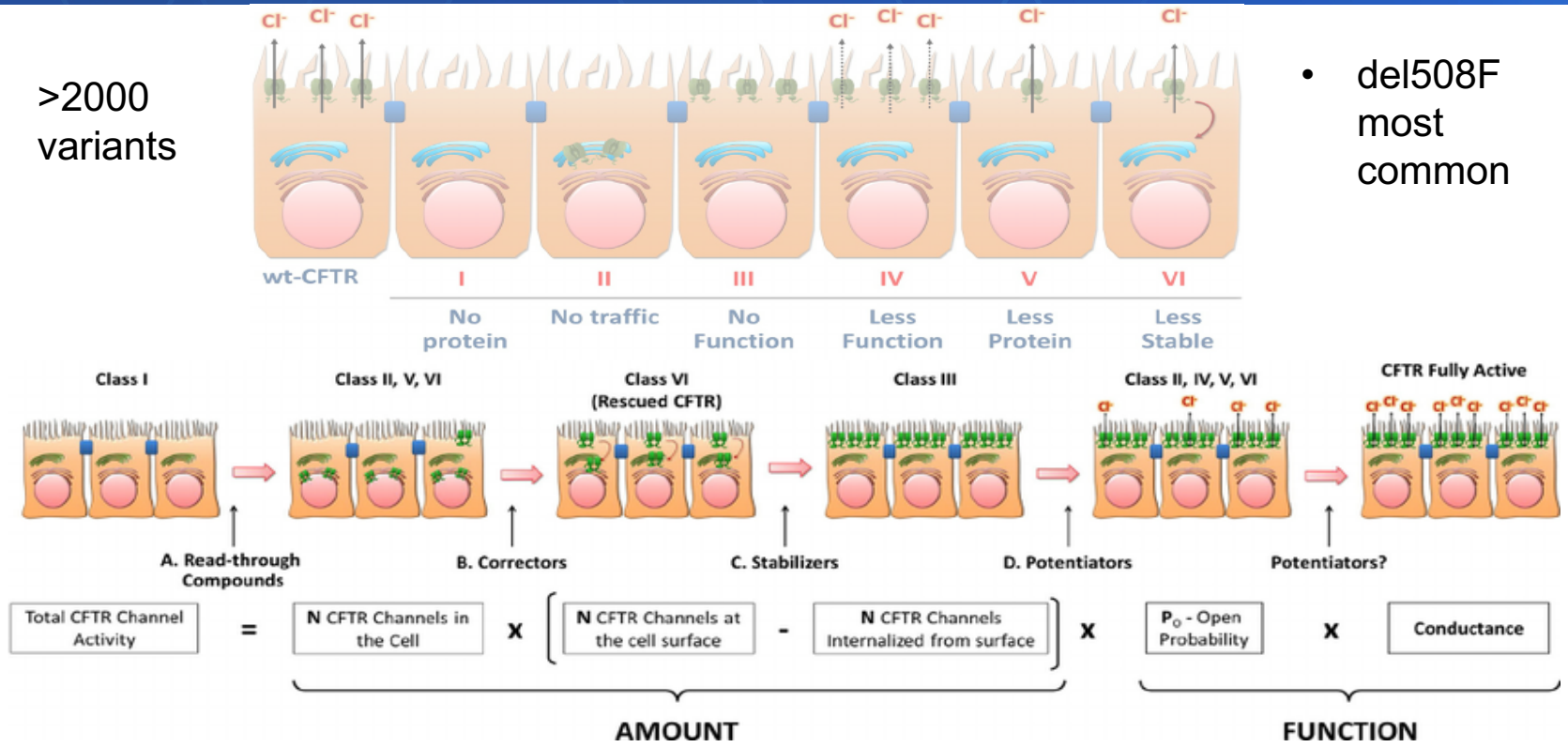
53 tissues from GTEx RNA-seq of 8555 samples/570 donors



UCSC Genome Browser on Human Dec. 2013 (GRCh38/hg38) Assembly – GTEx accessed 16Sept17

CFTR Mutations: Functional Effects

- >2000 variants



- del508F most common

Bell et al, Pharmacol Ther. 2015 Jan;145:19-34. PMID 24932877

22 ICP patients displaying evidence of a multi-genic inheritance pattern.

Patient	*PRSS1*	*SPINK1*	*CTRC*	*CFTR*
4	–/–	N34S/–	–/–	F508del/L967S
9	–/–	N34S/–	–/–	L967S/–
18	–/–	N34S/N34S	V235I/–	–/–
31	–/–	N34S/–	K247_R254del/–	R1162L/–
32	–/–	N34S/–	–/–	G542X/L188P
36	–/–	N34S/–	–/–	H1054D/G1069R
40	–/–	N34S/–	–/–	11TG-5T/–
48	–/–	N34S/–	R254W/–	–/–
49	–/–	N34S/–	–/–	F508del/E1124del
57	–/–	N34S/N34S	–/–	12TG-5T/–
68	–/–	–/–	C155Y/–	L997F/–
73	–/–	N34S/N34S	–/–	F508del/–
76	–/–	N34S/–	–/–	R117G/11TG-5T
77	–/–	N34S/–	–/–	F508del/S1235R
89	N29I/–	–/–	–/–	F508del/–
98	–/–	–/–	G217S/R254W	G85E/L568F
102	R122H/–	–/–	–/–	11TG-5T/–
110	N29I/–	–/–	–/–	G576A-R668C/–
115	R116C/–	N34S/–	–/–	–/–
125	–/–	[N34S;R65Q]/[N34S;R65Q]	–/–	G622D/11TG-5T
126	–/–	N34S/–	–/–	F508del/L206W
131	–/–	–/–	W55X/–	12TG-5T/–

Mulitgenic disease:
PRSS1
SPINK1
CTRC
CFTR

Masson E, Chen J-M, Audrézet M-P, Cooper DN, et al. (2013) A Conservative Assessment of the Major Genetic Causes of Idiopathic Chronic Pancreatitis: Data from a Comprehensive Analysis of PRSS1, SPINK1, CTRC and CFTR Genes in 253 Young French Patients. PLoS ONE 8(8): e73522. doi:10.1371/journal.pone.0073522

PLOS ONE

Analysis of *CFTR* and *SPINK1* variants in NAPS2 cases and controls – Bicarb Def. (BD)

984 cases and 1224 controls from NAPS2

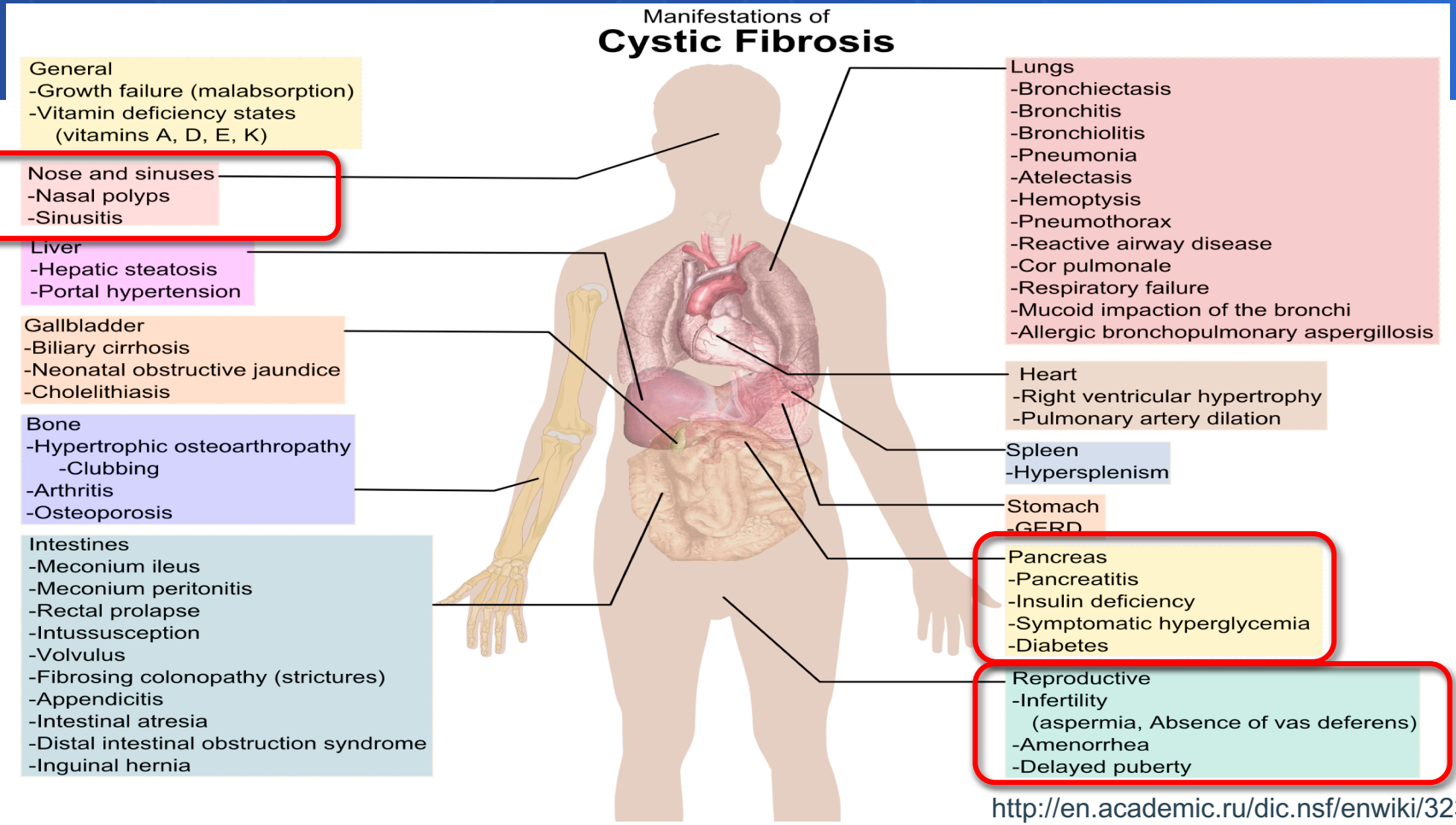
81 *CFTR* variants genotyped (CF mutations and reported in CP > 1)

43 variants were detected.

CFTR variant	%Cases	%Uctrls	OR	p-value	%Cases w/N34S	OR w/N34S	p-value w/N34S
CF/BD or BD/BD	2.5	0.0			5.5	7.46	0.12
All CF	8.7	3.3	**2.76**	**<0.0001**	16.4	**5.65**	**<0.0001**
F508del^{CF}	6.9	3.1	**2.32**	**<0.0001**	14.5	**5.13**	**<0.0001**
621+1G>T^{CF}	0.1	0.0		0.13	1.8		**<0.0001**
All BD	14.2	9.8	**1.50**	**0.002**	25.5	**4.63**	**<0.0001**
R75Q^{BD}	6.3	6.2	1.02	0.30	16.4	**2.97**	**0.003**
CF/BD or BD/BD	2.5	0.1	**31.9**	**<0.0001**	5.5	7.46	0.12
Other							
M470V	76.1	74.2	1.11	0.14	70.9	0.85	0.59
I148T	0.3	0.4	0.75	0.27	0.0	0.00	0.63

LaRusch et al *PLoS Genetics* 2014

CFTR: Bicarbonate conductance



http://en.academic.ru/dic.nsf/enwiki/32332

Integration & Application

Genetic Variables

- Susceptibility
  - ***PRSS1/2*** (risk and protective)
  - ***CFTR*** (5 classes)
  - ***SPINK1***
  - ***CTRC***
  - *CAP1*
  - *CASR*
  - *CEL*
  - *CLDN1*
  - *GGT1*
  - *ABO*
  - *MCP1*
  - *MTHFR*
- Modifier genes
  - Pain Genes
  - Phase I/II metabolism
  - Celiac
  - Dyslipidemia genes
  - Diabetes (multiple types)
  - Immune regulator genes
  - Other

Biomarkers

- AP/RAP
  - Amylase, lipase
  - CRP
- Imaging
  - CT
  - MRI / MRCP
  - EUS
  - ERCP
- Pancreatic function test
  - Secretin stimulation test
  - Serum trypsinogen
  - Fecal Elastase
  - Breath test / stool fat measures / others
- Pain measures
  - VAS
  - QOL
- Nutritional markers
  - Vitamin ADEK B12
  - Prealbumin, albumin
  - Weight, BMI Growth
  - Hemoglobin A1c, blood sugar,
- Experimental markers
  - Fibroscan
  - Urine biomarkers
  - Serum biomarkers
  - Other

Partial List!!

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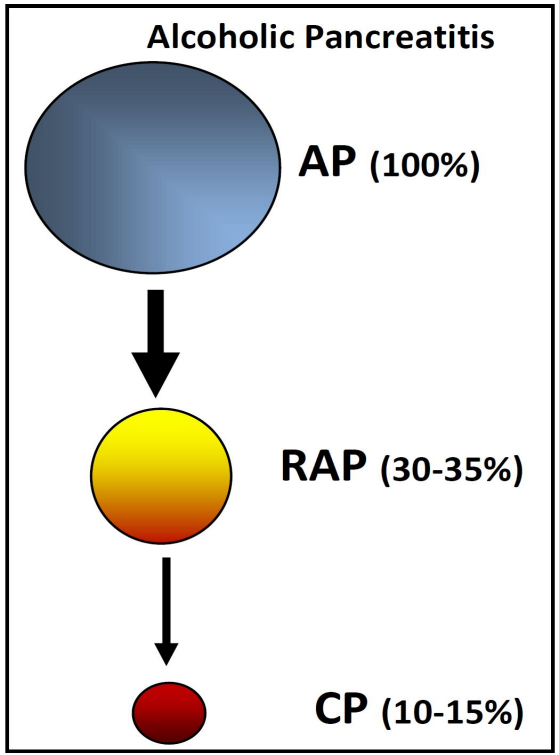
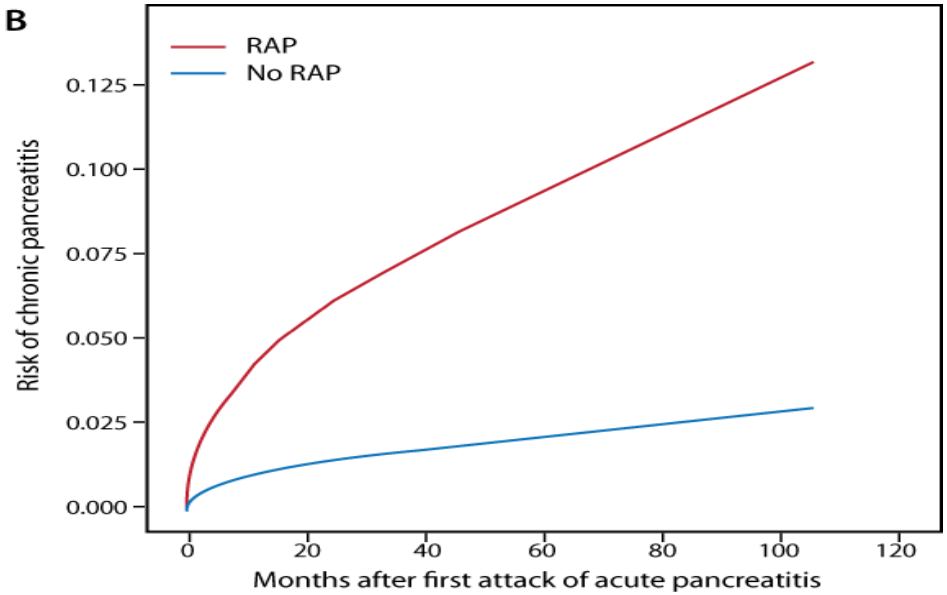
NEW DEFINITION & FRAMEWORK

Progression Model: Epidemiology



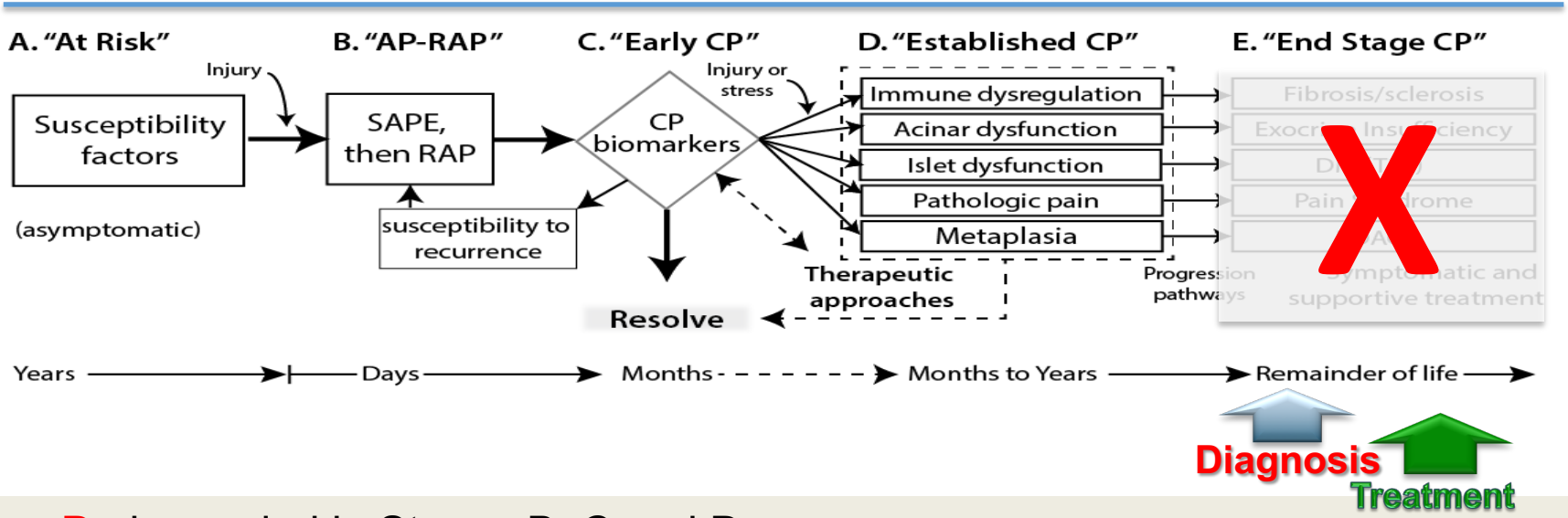
Yadav, Clin Gastroenterol Hepatol 2009;7:S15-7

RAP is a major the driver of CP



Yadav D, O'Connell M, Papachristou GI. *Am J Gastro*. 2012. [PMID: 22613906]

Early Diagnosis of CP (Mechanistic Definition)



- **Dx** is needed in Stages B, C and D.
- **Rx** should be started in Stages B, C and D.
- **Stage E** should be relegated to the history books.

AP-RAP, acute pancreatitis and recurrent acute pancreatitis; CP, chronic pancreatitis; DM (T3c), diabetes mellitus Type IIIc or pancreatogenic diabetes mellitus; PDAC, pancreatic ductal adenocarcinoma; SAPE sentinel acute pancreatitis event

The GOOD News

- New therapies can be based on genetic and mechanistic targets:
  - CFTR
  - PRSS1
  - Hyperlipidemia
  - Unfolded protein disorders
  - Oxidative stress mechanisms
  - Genes interacting with EtOH and smoking!
  - Obstruction
  - The future is not “genetics”,
    it is **personalized medicine**

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SUMMARY AND THE FUTURE

Summary:

- The Germ Theory of Diseases fails as a framework for complex diseases (e.g. chronic pancreatitis)
- “True” personalized precision medicine requires complex disease modeling
- ***Nobody*** can calculate all of the effects of all of the variables in their head (especially in 2-3 minutes)
- New tools are needed!
- **NEXT STEPS….**

HEALTH CARE POLICY

Ten things we have to do to achieve precision medicine

Major but surmountable hurdles should be addressed now to hasten the advent of precision medicine.

Kohane, Isaac S.
Science. PMID:26138968

- Linkage of health records
- Accuracy and reproducibility of data
- Connect research and clinical data sets
- Public approval of consent / data use
- Measures taken over a lifetime
- Perpetual updating of information
- Computer – driven real time decision support at point of care
- Affordability
- Representation for all ethnic and ancestral backgrounds
- Education of health workers – and **“in many instances, patients will be precision medicine experts ”**