Pankreatitis: autoimmune, hereditary…….

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Reiner Wiest M.D

Etiology based classification for recurrent acute/chronic pancreatitis

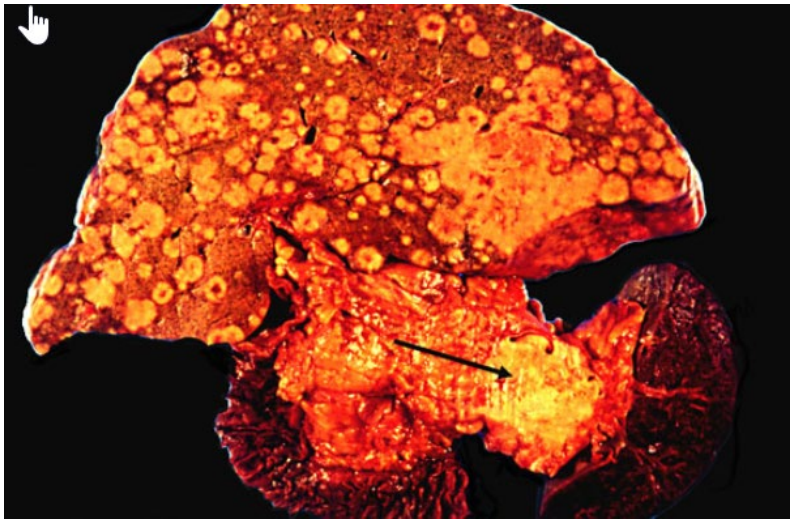
TIGARO-Classification:

T: Toxic-metabolic (alcohol, smoking….)
I: Idiopathic
G: ***Genetic***
A: ***Autoimmune***
R: Recurrent or severe acute
O: Obstructive

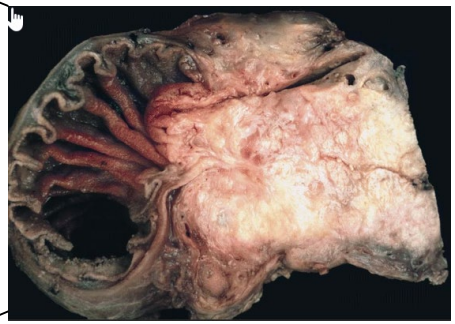
Etemad & Whitcomb. *Gastroenterology*, 2001.

What is more frequent: Pa-Cancer or AIP ?

Pancreatic Cancer



Far More Frequent than



AIP

->Thorough exclusion of cancer necessary before treatment of AIP

Does AIP resolve without intervention ?

Yes

in 10-20%

in asymptomatic patients watch-and-wait

(with monitoring)

is allowed

Two types of autoimmune pancreatitis

	Typ I (LPSP) Lymphoplasm. Scleros. Pancreatitis	Typ II (IDCP) Idiopath.ductocentr. Pancreatitis
Epidemiology *Age* *Gender*	Ca. 60% of AIPs M:W = 3:1 6th decade	Ca. 40 % of AIPs M:W = 1:1 4./5th decade
Clinic *Extrapancreatic involvment*	Jaundice 75% Acute Pancreatitis 5% YES	Jaundice 50% Acute Pancreatitis 33% NO
Association with IBD	Weak	Strong CED (v.a. CU) association (10-20%)
Treatment *Response*	**95-100%**	**90-100%**
Prognosis *Relapse Rate*	Up to 60%	<10%

HISORT means ? Stands for ?

H: Histology

I: Imaging

S: Serology

O: Other Organ Involvment

RT: Response to Treatment

Histology in AIP- differences in types ?

Feature	Typ I	Typ II
Lymphoplasmatic infiltration	Yes	Yes
Periductal inflammation	Yes	Yes
Storiform fibrosis	More prominent	Le
Obliterative Phlebitis	**Characteristic**	F
Granulocyte epithelial lesion (GEL)	Absent	**Characteristic**
IgG4 staining	**> 10/HPF**	Rare

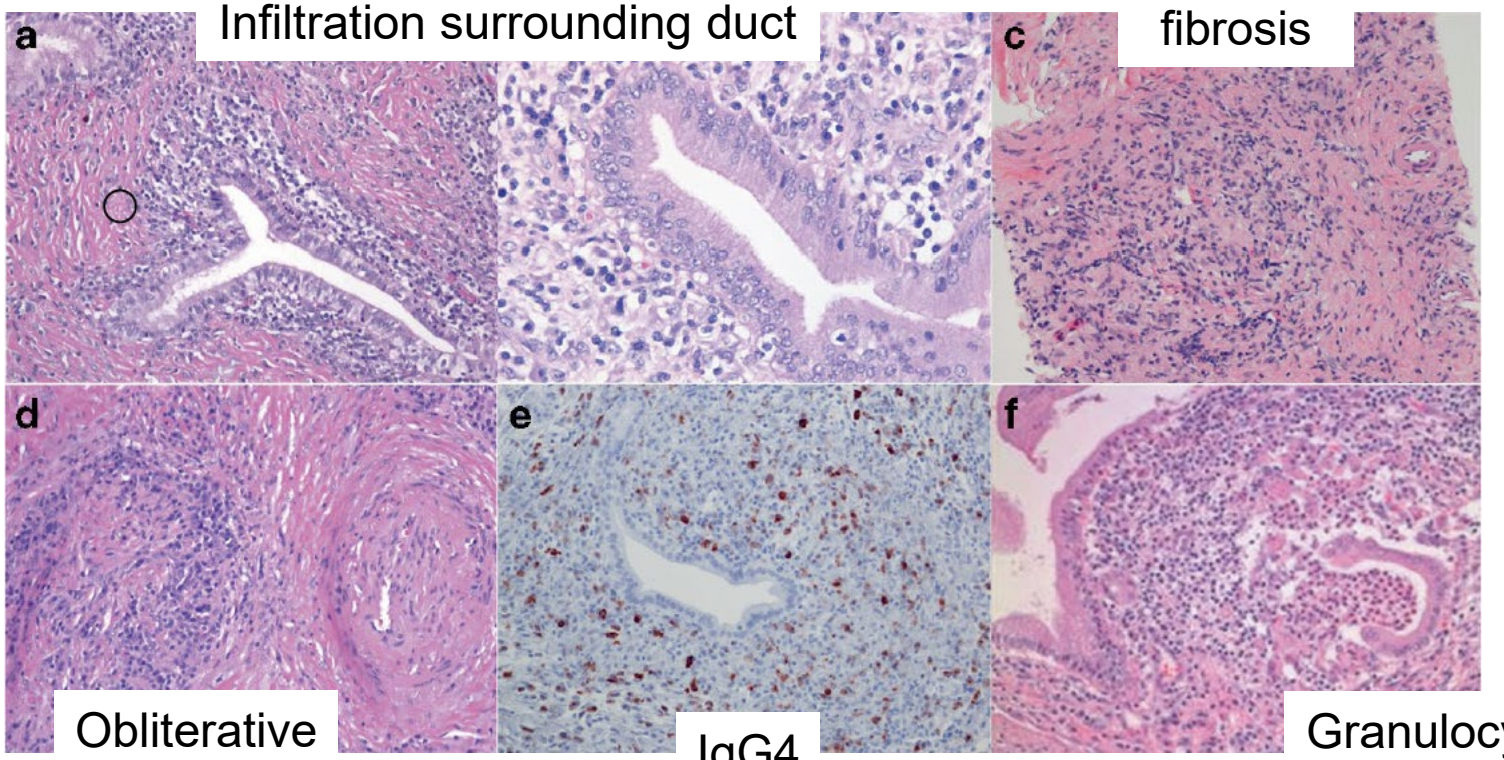
3 of 4 = Level 1

1or 2= Level 2

Histology in AIP- differences in types ?

Lymphoplasmacytic Infiltration surrounding duct

Storiform fibrosis

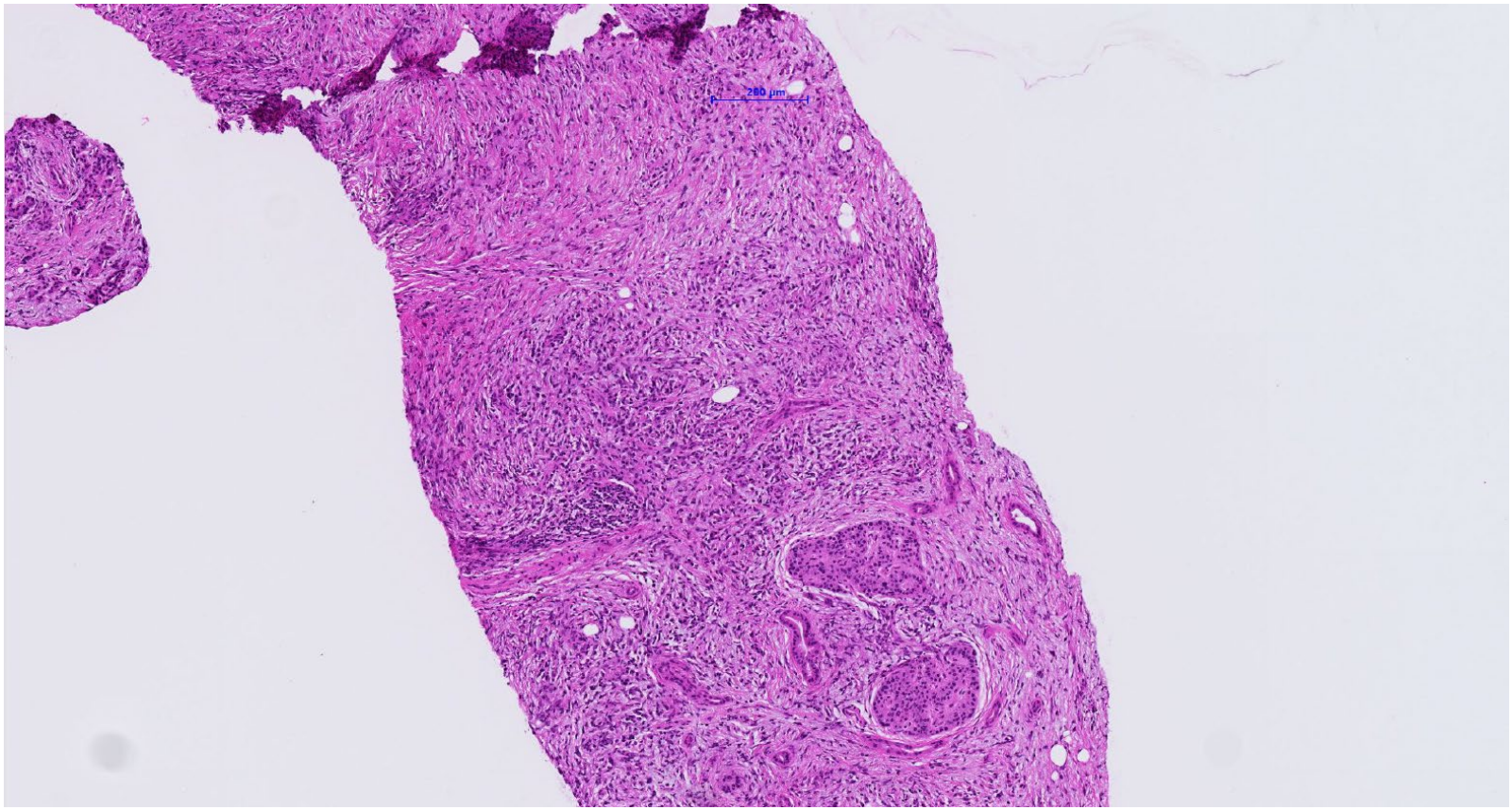


Obliterative phlebitis

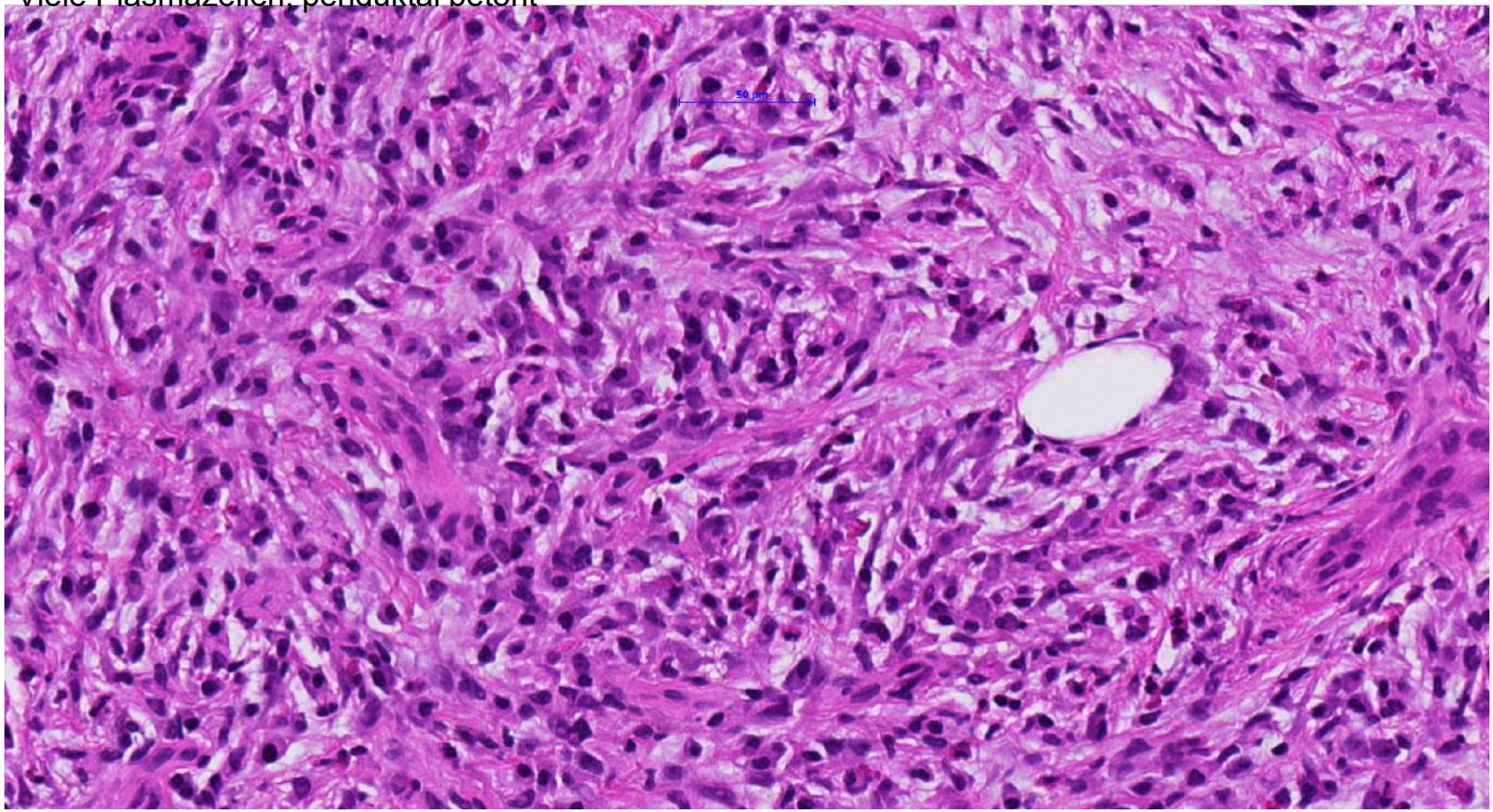
IgG4

Granulocyte Epithelial Lesion (GEL)

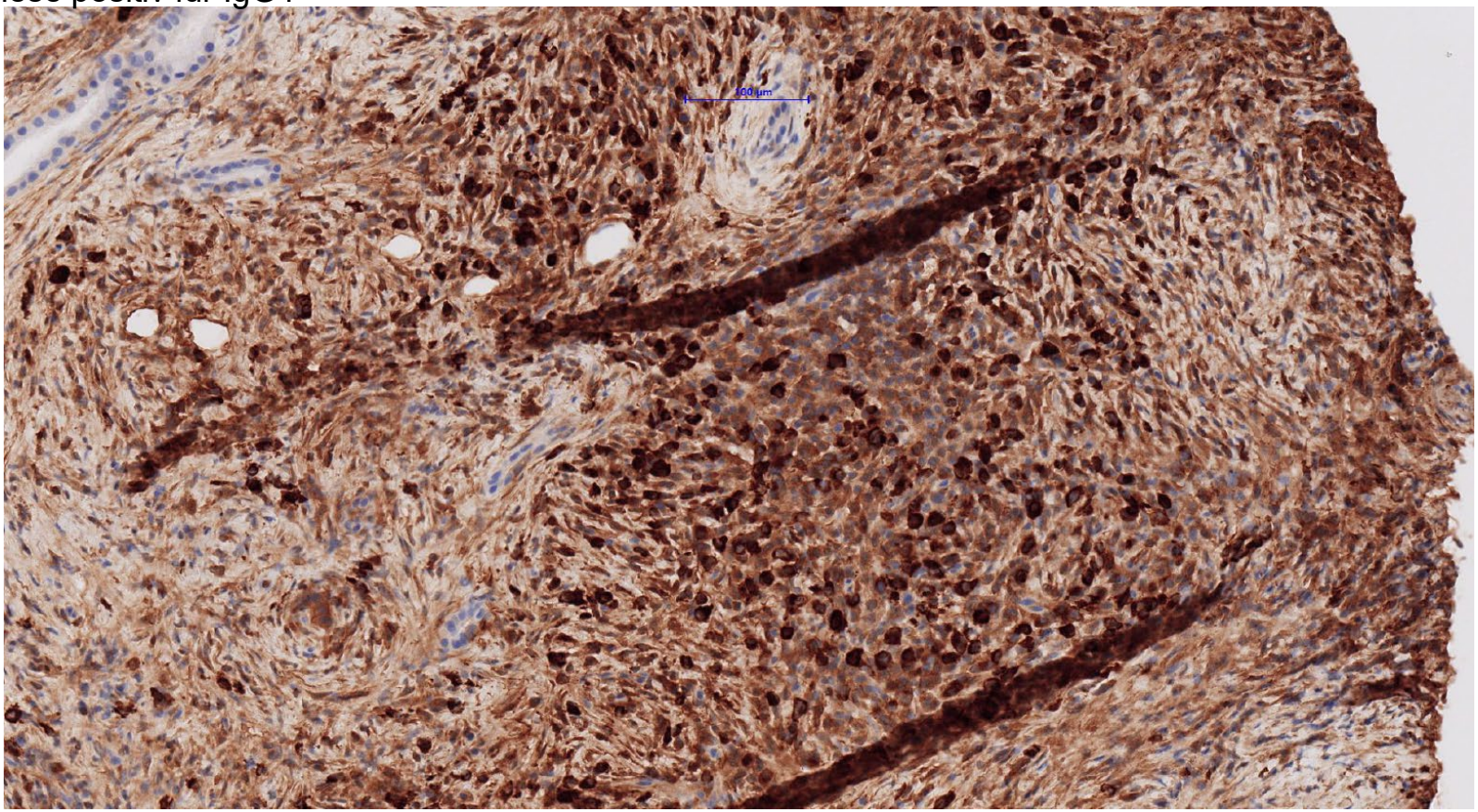
Übersicht Typ I AIP–
storiforme ‘wirblige’ Fibrose, atrophes Parenchym, zurückgeblieben praktisch nur noch endokrines Pankreas



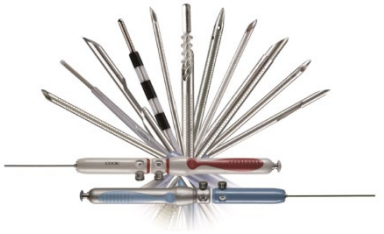
Viele Plasmazellen, periduktal betont



Diese positiv für IgG4



How to get best result for histo/cytomorphology ?

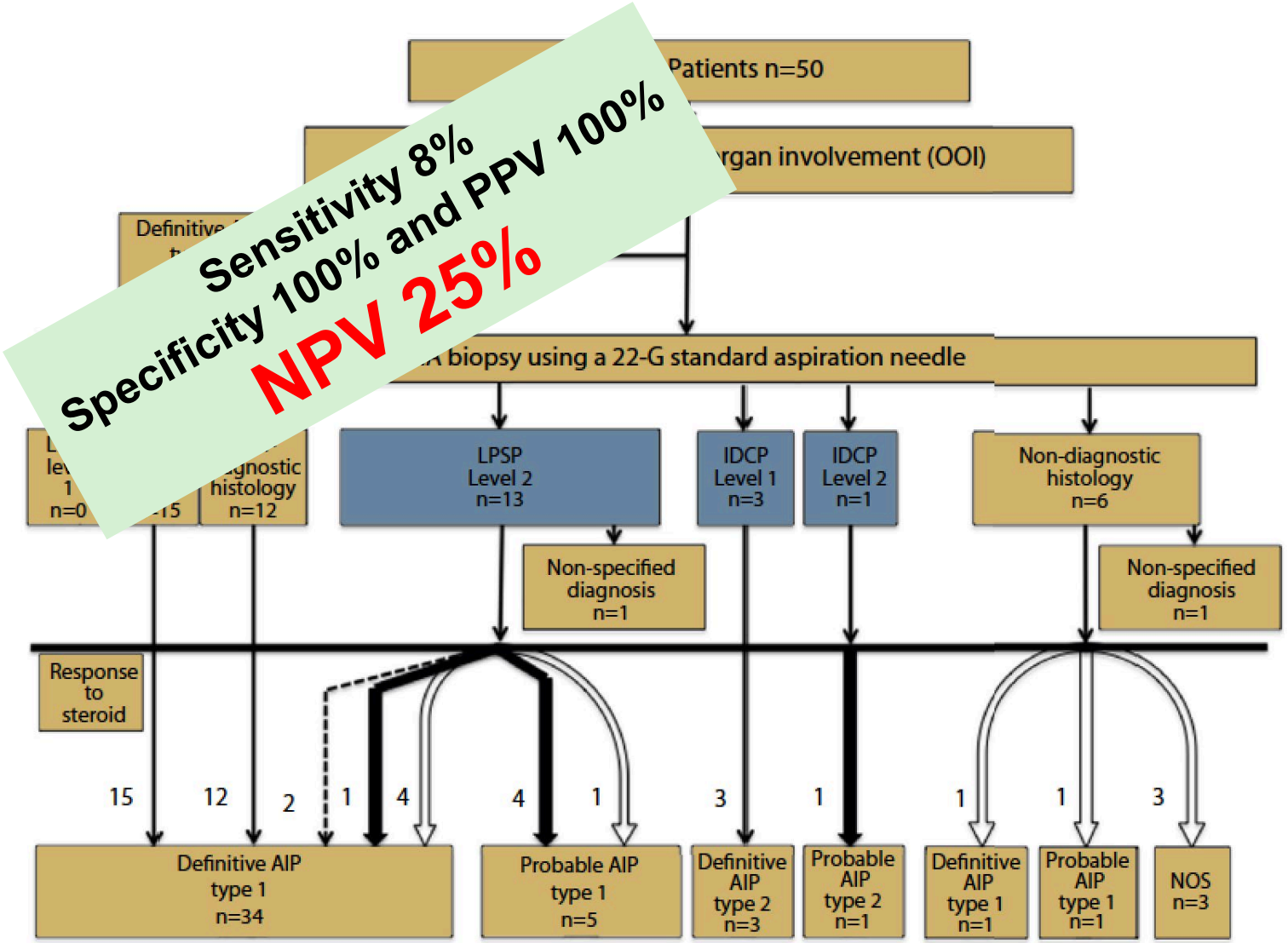


Level 1 histology diagnosis AIP:

- 19 G- FNA: 43%*
- True-Cut-biopsie in pediatric cases: 82% diagnostic yield°
- 22 G- FNA: 60% + up to 78% (Compas RCT-study)[1]

FNA for AIP very heterogenous results and….

- Iwashita T et al. CHG 2012 °: Fujii GIE 2013;
- + Kanno et al. GIE 2016 1: Kurita et al. GIE 2020



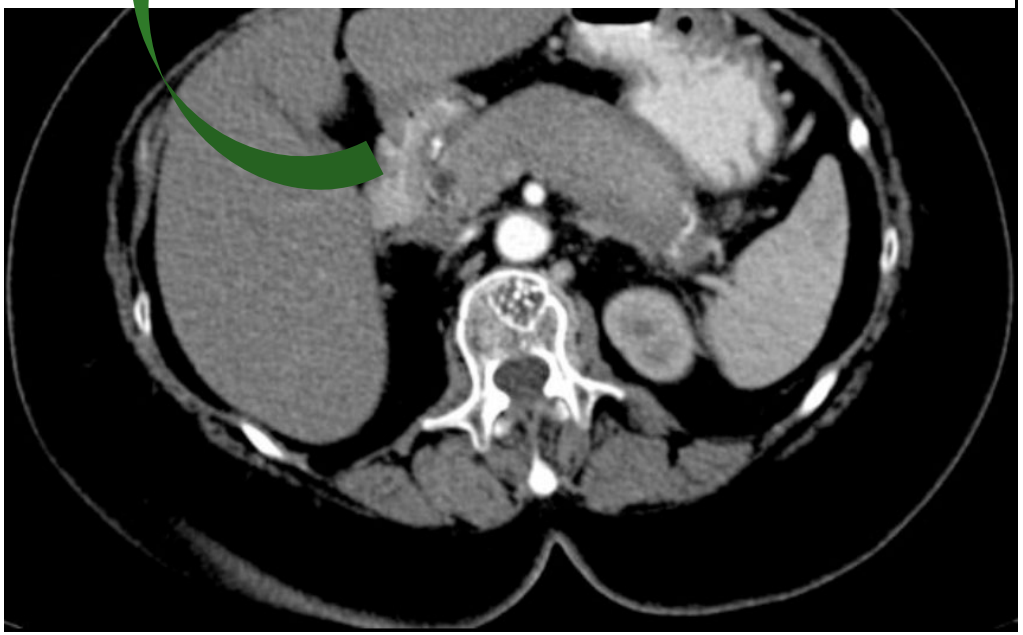
Sensitivity 8%
Specificity 100% and PPV 100%
NPV 25%

Morishima et al. GIE 2016

Imaging in AIP: characteristic features ?

Sausage-shaped pancreas
delayed contrast-enhancement in CT
Level 1 diagnostic for Typ I AIP

PS: rim-like capsule
In only 30-40%
but very specific

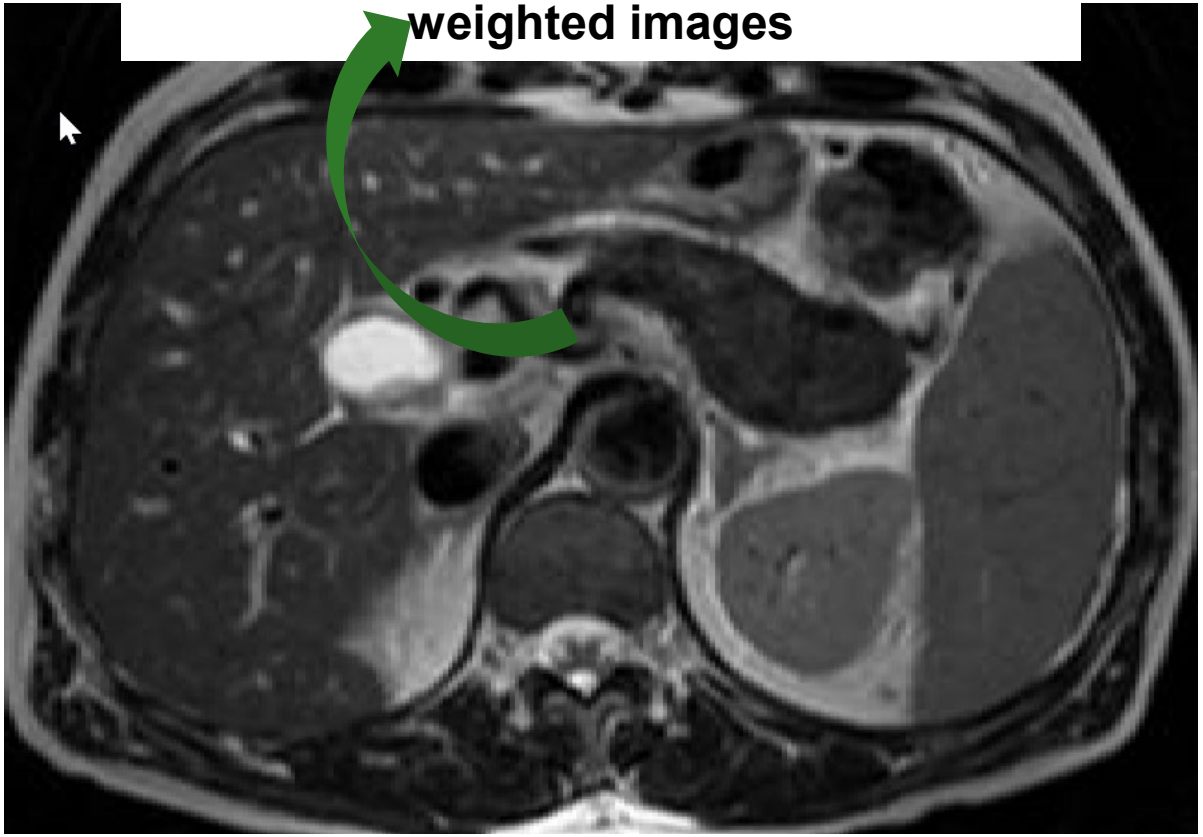


Level 2: Unclear focal/ mild

Level 1: = typical Pathognom.

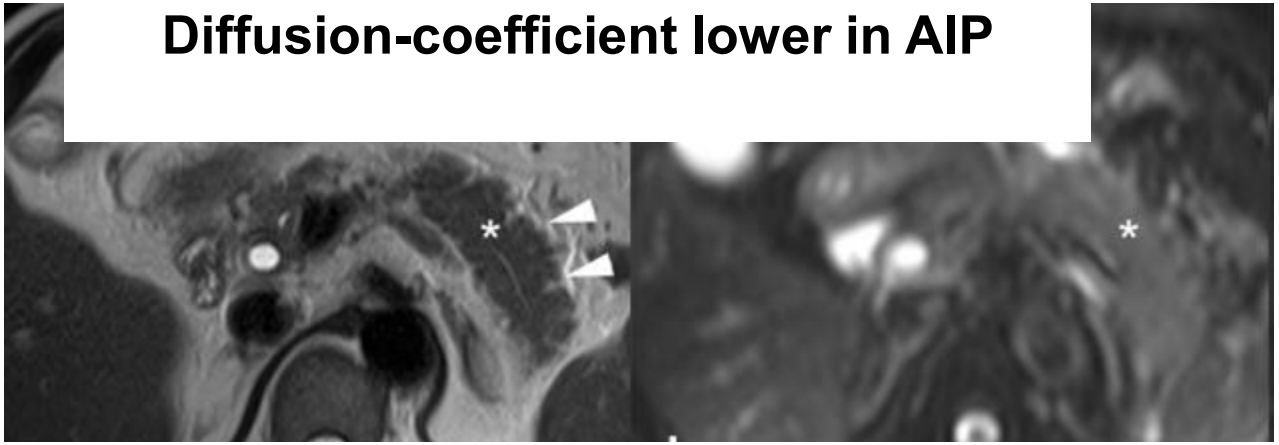
Imaging in AIP: characteristic features ?

NMR:
diffusely hypointense on T1-weighted images and slightly hyperintense on T2-weighted images

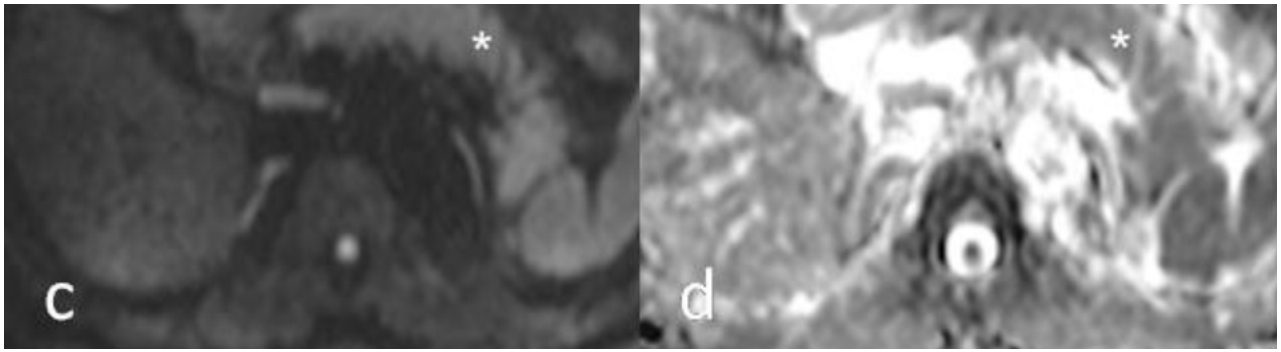


Imaging in AIP: characteristic features ?

Diffusions-MR
Diffusion-coefficient lower in AIP

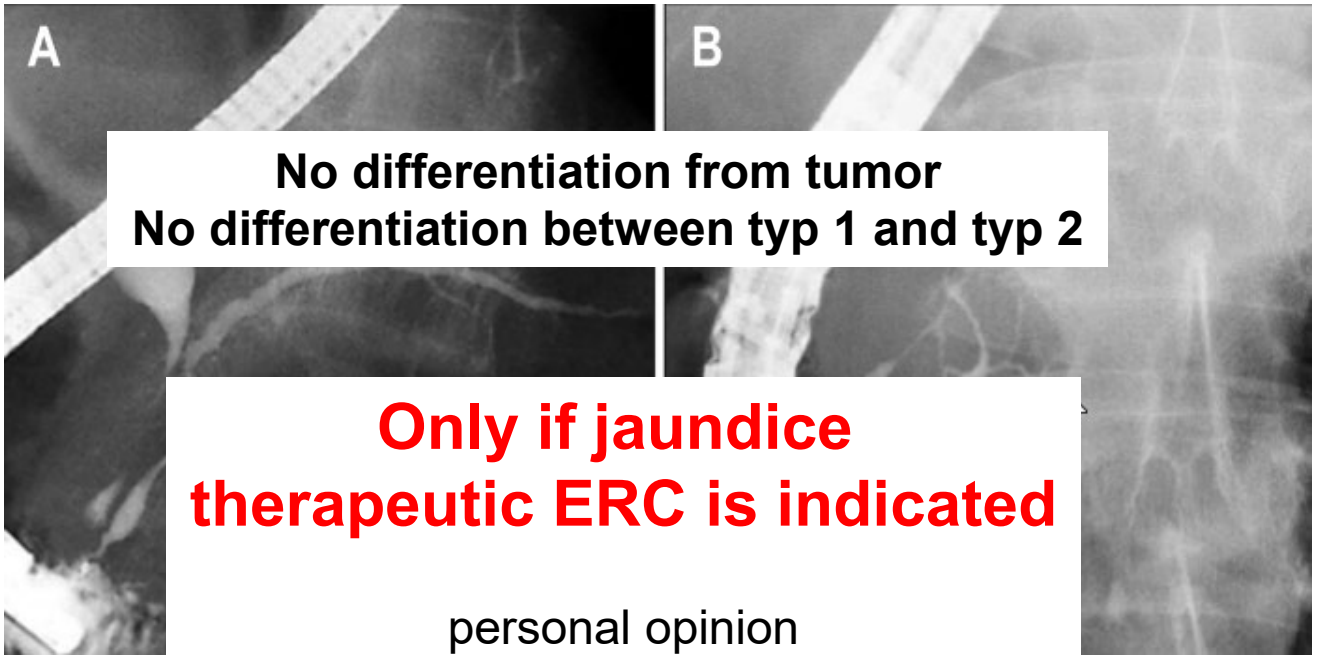


AIP (1.01 +/- 0.11 x 10-3 mm2/s)
pancreatic cancer (1.25 +/- 0.11 x 10-3 mm2/s)
normal pancreas (1.49 +/- 0.16 x 10-3 mm2/s)
(P<0.001)



ERCP for diagnosing AIP ?

main pancreatic duct
diffus narrowing or long (> 1/3 of PD) or multifocal strictures….



International Consensus Diagnostic Criteria (ICDC: Japan)
ERP-findings included (not usual in western countries)

If you do ERCP what to add/perform ?

Pancreatology 15 (2015) 259–264

Contents lists available at ScienceDirect

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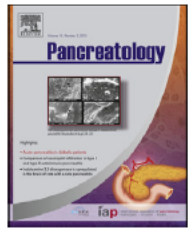
journal homepage: www.elsevier.com/locate/pan



Original article

Comparison of endoscopic retrograde cholangiopancreatography with papillary biopsy and endoscopic ultrasound-guided pancreatic biopsy in the diagnosis of autoimmune pancreatitis

Jae Gu Jung [a], Jong Kyun Lee [b, *, 1], Kwang Hyuck Lee [b], Kyu Taek Lee [b], Young Sik Woo [b], Woo Hyun Paik [c], Do Hyun Park [d], Sang Soo Lee [d], Dong Wan Seo [d], Sung Koo Lee [d], Myung-Hwan Kim [d, **, 1]

Papilla biopsy
increased diagnostic sensitivity
from 65%
to 95%

Other organ involvement AIP-Typ I- which ones ?

Level 1: both a) and b)

a) min. 3 of following histological parameter

In other organs than pancreas:

- lymphoplasmacell.infiltrate and fibrosis (sine granulocytes)

- **Storiform fibrosis**
- **Obliterative phlebitis**
- **IgG4-positivity (> 10/HPF)**

b) min. one of following radiological parameter:

- segmental/multiple proximal biliary strictures

- Retroperitoneal fibrosis

Absence of extrapancreatic (other organ) involvment does rule out Typ I AiP?

No

about 50% are isolated pancreatic manifestation

Serology ?

Liver encymes, cholestasis markers, lipase

Typ I	Typ II
IgG4-Titer increased increased ANA-, RF, Gamma-Globulinemia	IgG4 normal almost no alterations

IgG4 increased:
> 2-times normal = Level 1

1-2-fach = Level 2

NPV 98%
Carcinom: up to 10% increased
(ca. 1-7% also > 2-fach)
The higher the more predictive
> 2-fach: > 90% Spezfisch

AIP: Response to treatment – which – how ?

- **Corticosteroid: 0.6-1 mg/kg KG**
- **Mayo-Schema: 4 weeks 40 mg/d, then taper 5mg/week (over 8 weeks)**

- **Control after 2 (or 4 weeks): IgG4, CA19-9 and**

Repeat imaging after 2 (or 4 weeks): cave: inflammation resolves

But can take also more weeks to months (fibrosis remains if present)

Contraindications for steroids – alternatives ?

Rituximab as first line therapy

Aza/Thiopurine suboptimal for induction of remission

Rescue medication

case reports on cyclosporine or rapamycin

Maintenance treatment to prevent relapse

When do you think you do not need (strictly) maintenance therapy ?

When low disease activity =

- ✓ **Pancreas only/ no other organ involvments**
- ✓ **Complete radiological response short-term (4 weeks)**
- ✓ **Complete normalization of IgG4 short-term**

then 3 months course sufficient

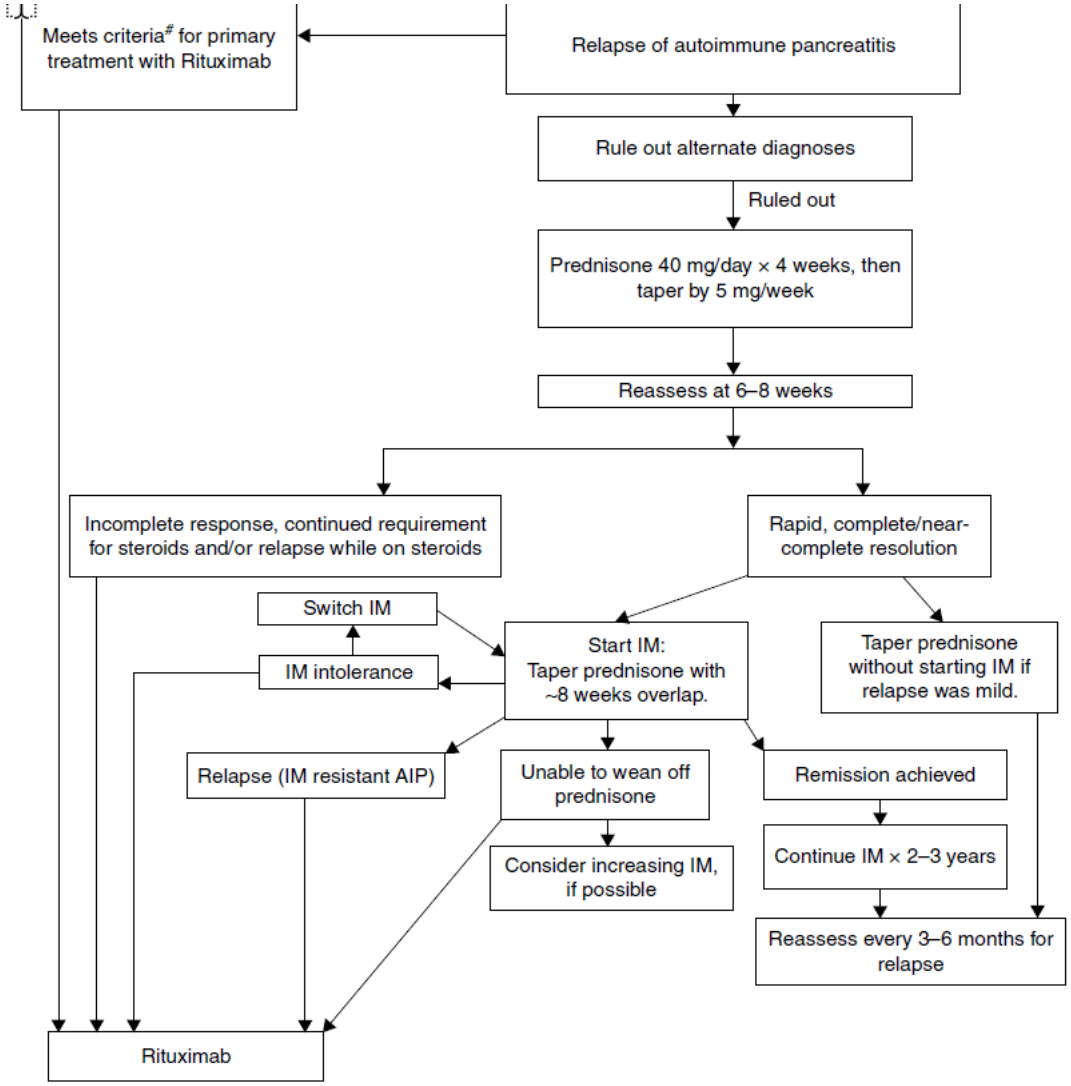
(4 weeks 40mg tapered off then in 8 weeks)

When mantenance treatment to prevent relapse ?

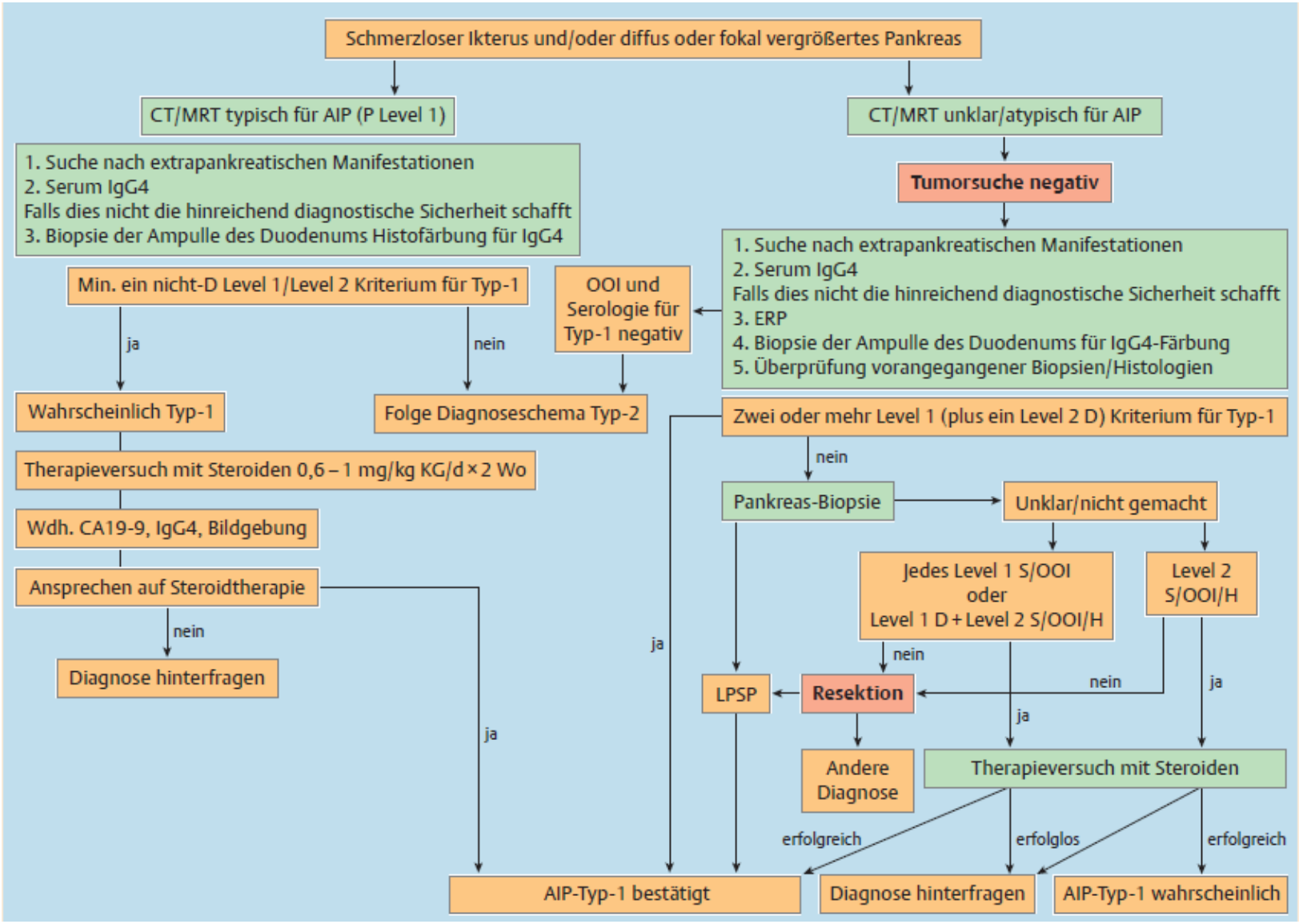
Risk factors for relaps after steroid stop

- young age
- diffuse pancreatic swelling and delayed radiological improvement
- extrapancreatic biliary involvement (IgG4-AIC)/icterus, high AP
- Very high IgG4 (> 4-times normal) and persistend during steroid therapy
- ≥ 2 OOI

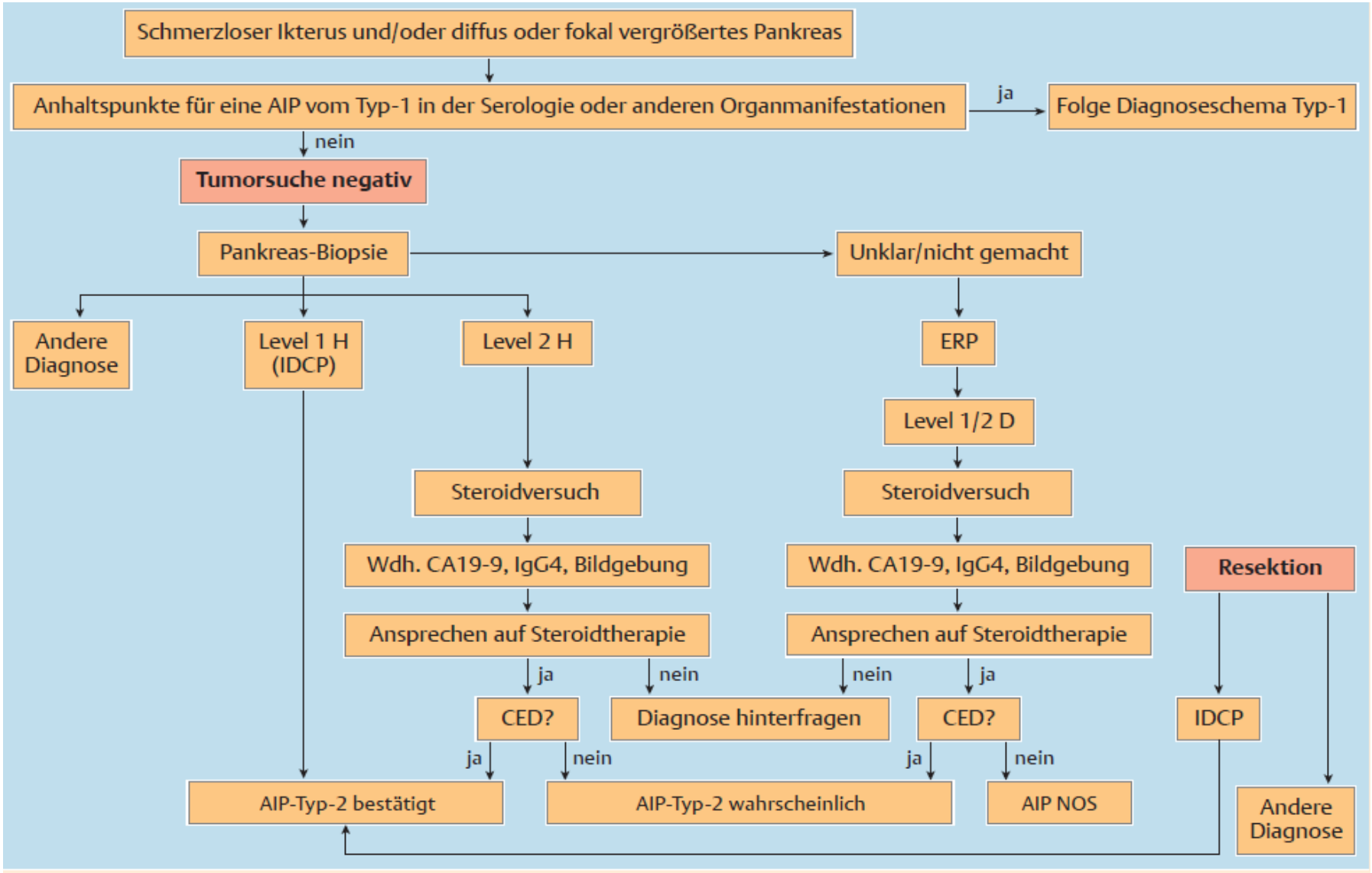
Relapse in AIP – algorythm ?



TypI: Autoimmun-Pankreatitis



Typ-II: Autoimmune-Pancreatitis



Genetics of the Pancreas
Hereditary Pancreatitis and Risk of Cancer

Key Points in Genetics: Basic Knowledge

- Pathogenic genetic variants act by:
  - Altering protein **expression**
  - Altering protein **location**
  - Altering protein **function**
    - Loss of function
    - Gain of function
    - Change of function

- Pathogenic genetic variants cause disease by:
  - Altering normal **development** (congenital)
  - Altering **function** (congenital or acquired)
  - Altering **responses** to stress or injury (acquired)

Definition of hereditary pancreatitis ?

- **Presence of chronic pancreatitis in two first – degree or three second degree relatives in two or more generations, without precipitating factors and with a negative work-up for known causes**

- **Detecting a causative gene mutation**

Which genes- when mutated affect risk for HP ?

- SPINK1: Serin-Protease-Inhibitor-Kazal-Typ 1= SPINK
- PRSS-cationic trypsinogen gene
- CTRC: Chymotrypsinogen-C
- CFTR: cystic fibrosis transmembrane conductance regulator
- Calcium-sensing receptor Gene
- Claudin-2 (CLDN2)
- Carboxypeptidase A1 (CPA1)
- ….

In children genetic etiology of pancreatitis is found how frequent ?

In previously diagnosed

- **Idiopathic acute** **33%**
- **Recurrent acute** **45%**
- **Chronic pancreatitis** **55%**

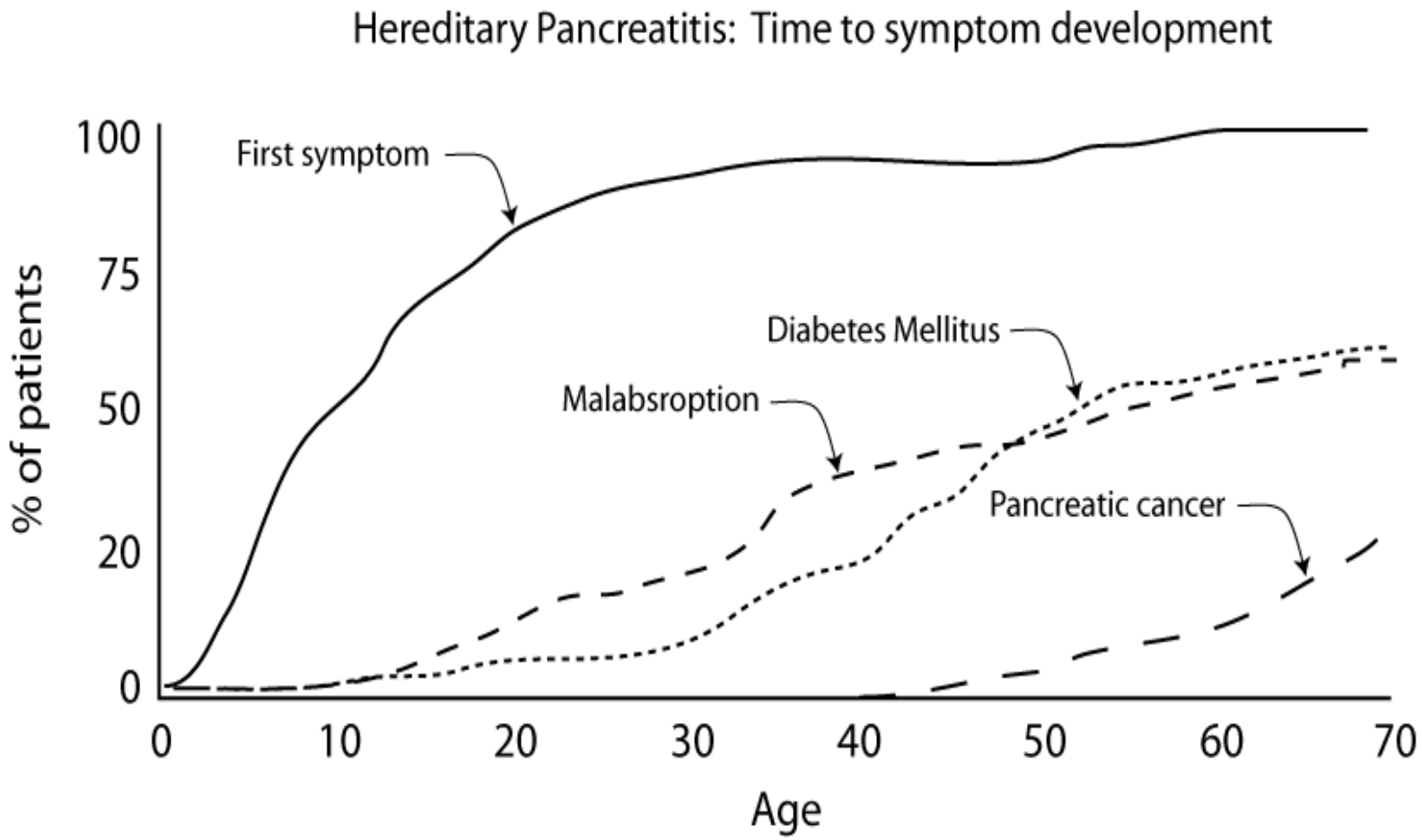
HP is one of the main causes of pancreatitis in children

Special clinical relevance of hereditary pancreatitis…

Cumulative risk of

- **Exocrine insufficiency** — **60%**
- **Diabetes** — **68%**
- **Pancreatic cancer** — **To be anounced**

Natural History of hereditary pancreatitis



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

Risk of pancreatic cancer in HP ?

- **standardized incidence ratio 50-87**
- **cumulative risk until age 70: 40%**
- **low below age 50**
- **needs decades after first clinical presentation**
- **smoking doubles risk –occurence about 20 years earlier**
- **diabetes add-on risk factor**

Number of first and second degree relatives with CA
e.g. two first degree – life time risk about 8 %

Genetic testing ? When – whom to consider ?

Before performing molecular analysis- genetic counseling

Consider genetic testing for HP when

- **Family history of idiopathic CP, recurrent pancreatitis or**
- **Childhood pancreatitis (or < 25 years in age with recurrent acute pancreatitis or CP) without explanation after extensive work-up**
- **Relatives with known mutations associated with HP**

What you know about SPINK1 ?

SPINK1 is an acute phase protein and specific trypsin inhibitor

Few SPINK1-mutations directly associated with HP: autosomal-recessive

One SPINK1-mutation (c.27delC) inherited autosomal dominant

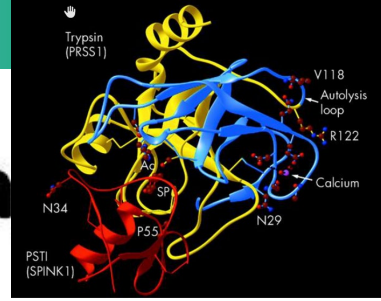
Majority inherited in heterocygous form

Phenotypic expression of pancreatitis requires interactions with

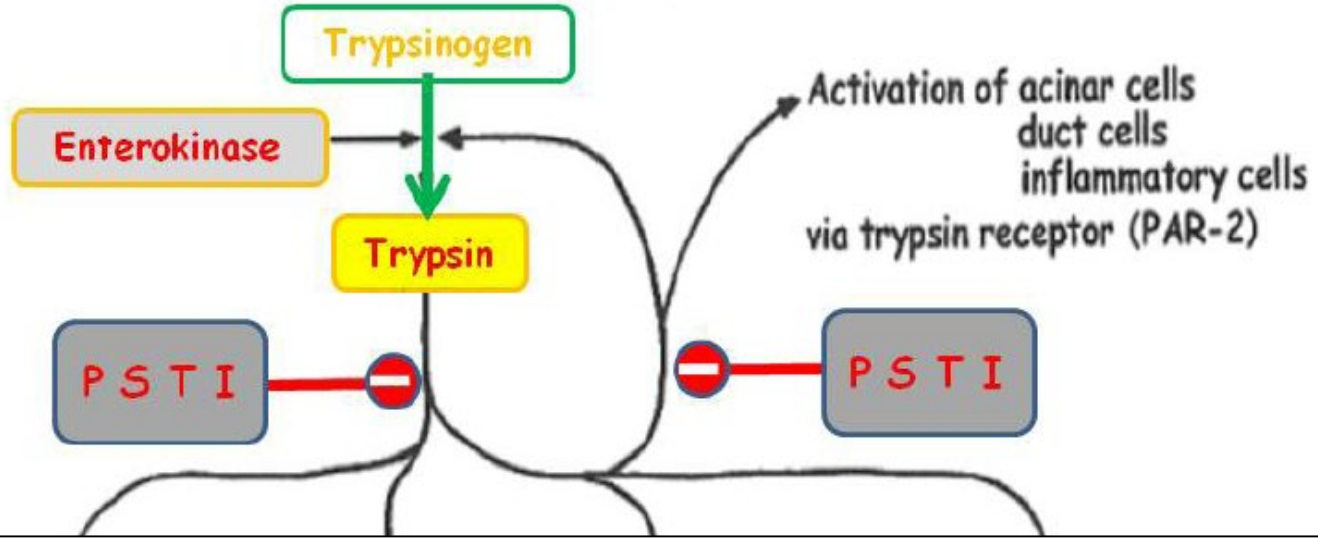
Other genetic mutations and/or environmental factors

= *disease-modifying mutations*

Mutations in SPINK1 in HP

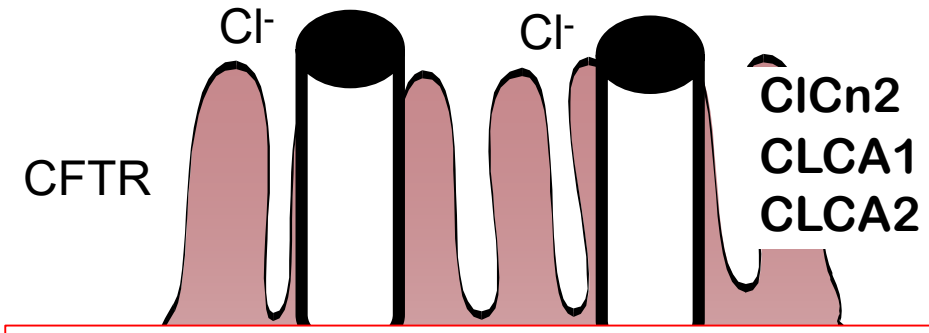


- **PSTI** Pancreatic Secretory Trypsin-Inhibitor
  - Serin-Protease-Inhibitor, Kazal-Typ 1: **SPINK1**



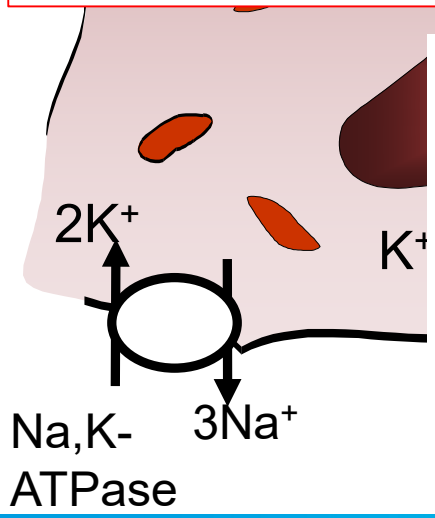
In pancreas: inhibits up to 20% of trypsinogen
e.g. mutation: L14R in 2 european large families:
rapid intracellular degradation of the mutant protein=
abolished secretion of SPINK1

Pathophysiology cystic fibrosis ?



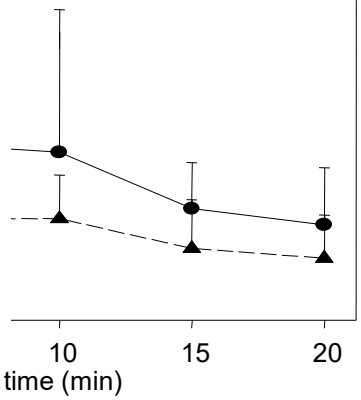
- Mutation des CFTR Chlorid-Kanals
- damit Störung der Sekretion von Chlorid-Ionen und Bildung eines zähen Sekrets
- Prävalenz 1:2500, heterozygot: 1:25

CFTR in pancreas = primary molecule in bicarbonate conductance



WINK1/SPAK activation changes CFTR from a chloride- to a bicarbonate-preferring channel

NKCC1



CFTR and clinical presentation

- **Cystic Fibrosis (of the pancreas)**
  - Clinical syndrome(s)
    - **Classic CF**: pancreatic insufficiency, abnormal sweat chloride, progressive lung disease, meconium ileus, male infertility (CBAVD), liver disease.
    - **Atypical CF**: like CF but milder symptoms
    - **CFTR-Related Disorders**: (CFTR-RD)
      - Recurrent acute & chronic pancreatitis (CFTR + SPINK1)*
      - Pancreatitis, male infertility, chronic sinusitis (CFTR-BD**)
  - Genotype: $CFTR^{x}/CFTR^{X}$ (x = $CFTR^{sev}$, $CFTR^{mv}$ or $CFTR^{BD}$)***
  - Diagnosis: Clinical features, + Sweat chloride or nasal potential difference + abnormal *CFTR* genotype.
  - Consider referral to a CF Center to make the diagnosis.

* *CFTR/SPINK1* genotypes represents a complex disorder
** BD, bicarbonate conductance defective.
*** functional effects on CFTR function, sev=severe, mv=mild variable

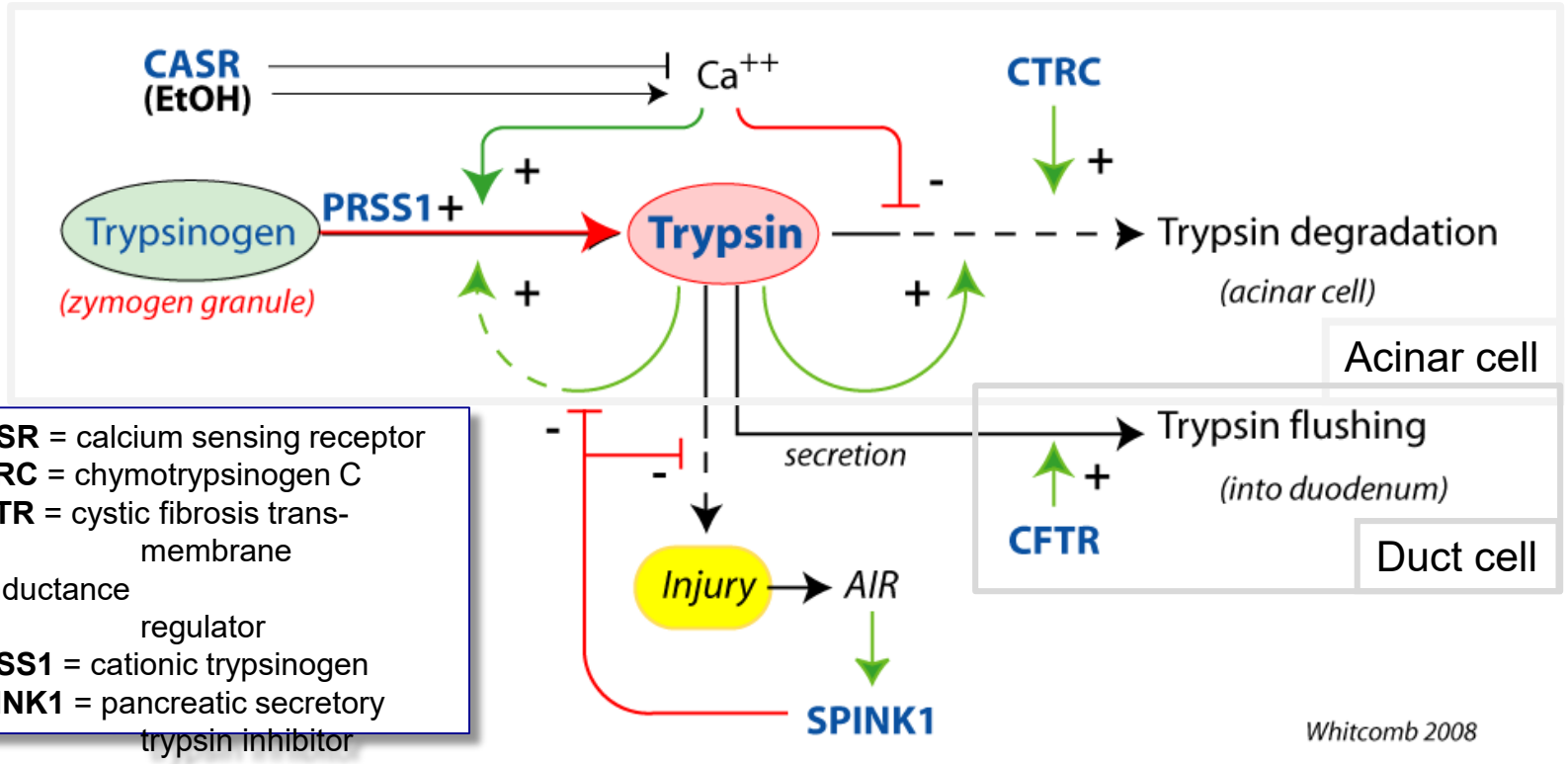
Chymotrypsinogen-C: CTRC ?

- relatively rare (1-3% of HP)
- degrades Trypsin
- mutations with loss of function

  (reduced CTRC-secretion or catalytic defect within CTRC-protein)

  ->increase Trypsin-action
- confer increased risk for pancreatitis in interaction with
- SPINK1, CFTR-mutations and/or environmental factors
- increased risk by 4-8 fold for pancreatitis

Genetic Variants Related to Trypsin



CASR = calcium sensing receptor
CTRC = chymotrypsinogen C
CFTR = cystic fibrosis trans-membrane conductance regulator
PRSS1 = cationic trypsinogen
SPINK1 = pancreatic secretory trypsin inhibitor

AIR = Acute inflammatory response (acute phase protein expression)

- Genes linked to **CP susceptibility** all regulate intra-pancreatic **trypsin** activity.
- Both the acinar cells and duct cells are linked with pancreatitis-causing variations

Whitcomb DC. *Annu Rev Med*. 2010;61:413-24.

PRSS-associated hereditary pancreatitis: progression and CA?

autosomal dominant

penetrance 80%

+FA: Pancreatitis attacks from childhood on

Progression to chronic pancreatitis

forcified by alcohol and nicotin

Risk for pancreatic cancer: 50j: 10% at age 75: 50%

Alcohol and acute pancreatitis ?

Bier

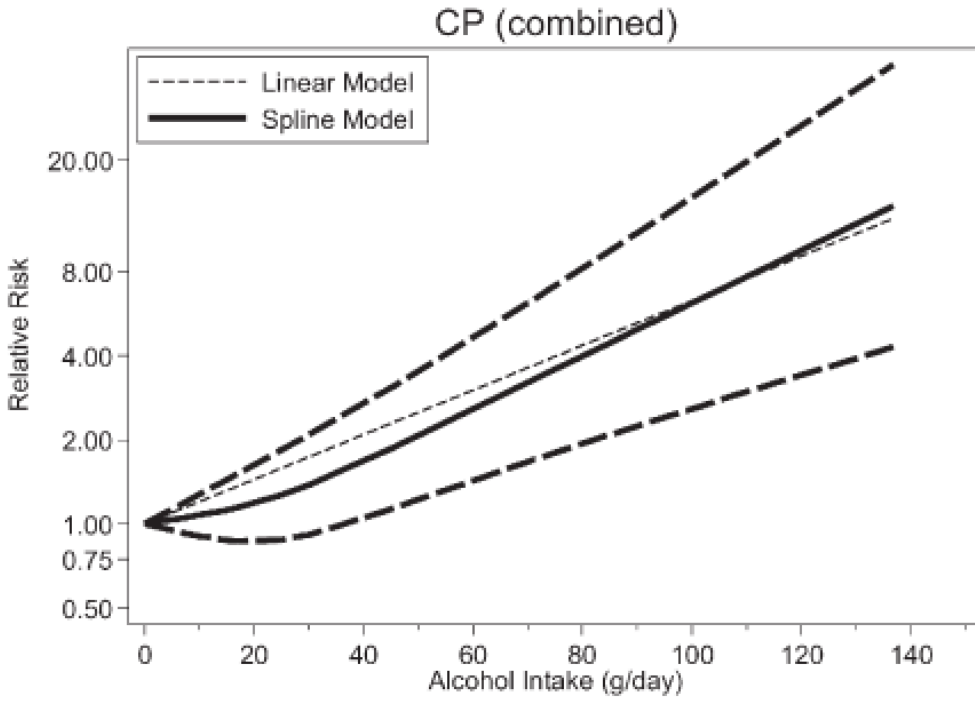
ALCOHOL

- No threshold below which no pancreatitis is caused or triggered
- Dose: Risk of pancreatitis increases with dose
- 5% of «heavy drinker» (> 80g/d for > 10 y) develop chronic pancreatitis

Amann RW et al. Pancreas 1997

Alcohol and Pancreatitis

Alcohol Consumption as a Risk Factor for Acute and Chronic Pancreatitis: A Systematic Review and a Series of Meta-analyses



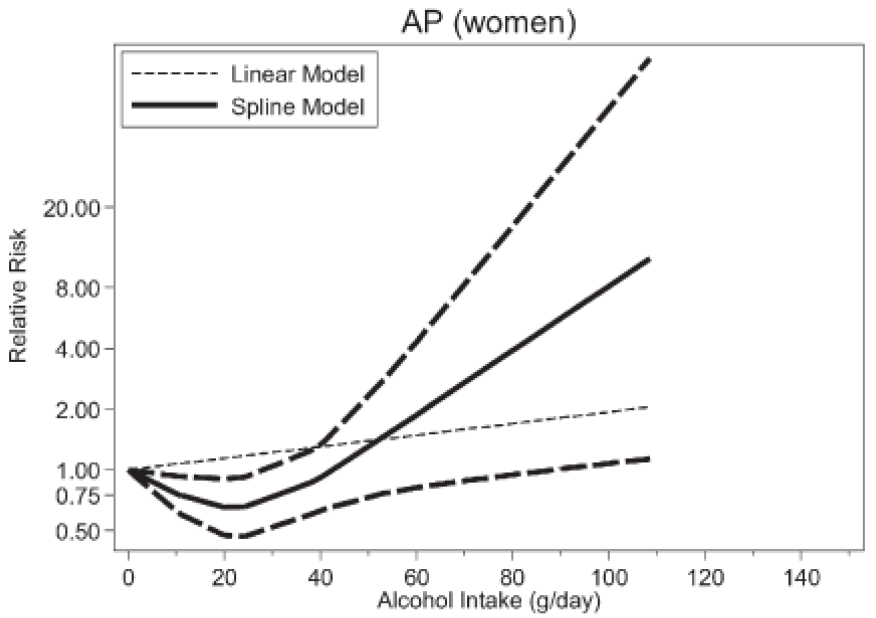


Fig. 4. Pooled dose–response risk relationships between average alcohol consumption and acute pancreatitis in women.

Samokhvalov et al. EbioMed 2015

C2 + Nikotin and Pancreatitis

	Alcohol consumption (g/month)			
	<400		≥400	
	RR† (95% CI)	p Value	RR (95% CI	
Smoking status*				
Never	1 (Ref)			
Former	1.30 (0.88 to 1.90			0.02
Current	1.63 (1.0		.19)	<0.01
Pack-years of				
N			1 (Ref)	
	.06)	0.20	1.97 (0.91 to 4.24)	0.08
	(0.81 to 2.55)	0.21	3.96 (1.87 to 8.39)	<0.01
<20	1.69 (0.99 to 2.90)	0.06	2.13 (0.84 to 5.40)	0.11
≥20	1.94 (1.18 to 3.19)	<0.01	4.12 (1.98 to 8.60)	<0.01

After two decades of smoking cessation risk of non-gallstone-related acute pancreatitis is reduced to a level comparable to that of never smokers

Gut 2012 O-Sadr

Who should undergo surveillance for pancreatic cancer development ?

- **All patients with Peutz-Jeghers (germline LKB1/STK11 mutation)**
- **All carriers germline CDKN2A mutation**
- **Carriers of germline BRAC2, BRCA1, PLAB2, MLH1, MSH2 or MSH6 and one FDR**
- **Individuals who have at least one FDR with PDAC (and in turn a FDR+ PDAC)**

Positive family history for = high risk for pancreatic cancer is when ?

PA-Cancer in at least one first degree relative and either

- **2 relatives on same side or**
- **2 relatives who are first degree related to each other**

Surveillance for pancreatic cancer at which age ?

Positive family history – without germline mutation known/found:

-then start at age 50 (or 55) or

-10 years younger than youngest affected relative

Mutation carrieres: depends on mutation, namely

CDKN2A or Petz Jegher Syndrome start at age 40

BRAC2, ATM, PALB2, BRCA1, MLH1/MSH2:

-start age 45 (or 50) or

-10 years younger than youngest affected relative

How to perform surveillance for pancreatic cancer ?

At baseline:

MR/MRCP + EUS + fasting glucose (and/or HbA1c)

Follow-up:

alternate MR/MRCP and EUS, routinely fasting glucose (and/or HbA1c)

On indication:

Serum CA19-9 (if imaging shows concerning features)

EUS-FNA

solid lesion (> 5mm), cystic lesion + worrisome features, MPD strictures

CT

solid lesion (regardless of size) or MPD stricture of unknown etiology

What should you eat to treat your pancreas well ?

ORIGINAL ARTICLE

Vegetables, fruit and risk of non-gallstone-related acute pancreatitis: a population-based prospective cohort study

Viktor Oskarsson,[1] Omid Sadr-Azodi,[1,2] Nicola Orsini,[1] Åke Andrén-Sandberg,[2] Alicja Wolk[1]

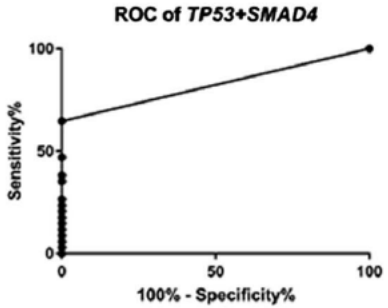
Gut 2017

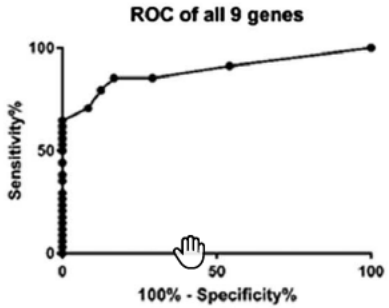
OPEN ACCESS

ORIGINAL ARTICLE

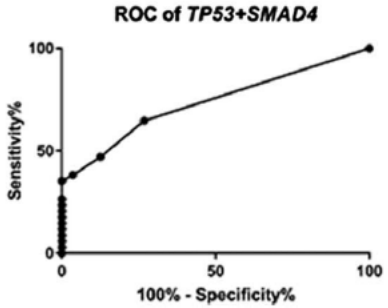
Digital next-generation sequencing identifies low-abundance mutations in pancreatic juice samples collected from the duodenum of patients with pancreatic cancer and intraductal papillary mucinous neoplasms

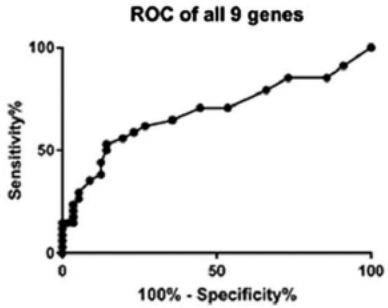
PDAC vs Control





PDAC vs IPMN





THANKS FOR YOUR ATTENTION

ADD-ON OPTIONAL

Complex Genetics

Pathogenic genetic variables that are neither sufficient nor necessary to cause a disease, but that come together with other factors (genetic or environmental) to increase *susceptibility* to a condition, or to *modify* its clinical features.

- Gene x Environment: (e.g. CLDN2 + alcohol)
- Gene x Gene: (e.g. CFTR + SPINK1)

otherwise mild cystic fibrosis syndrome.[57] Finally, some CFTR mutations can be inherited in a complex-type pattern. When a patient is heterozygous with, for example, one *CFTR* mutation and an additional genetic mutation, such as *SPINK1* or *CTRC*, the risk of pancreatitis is increased.[26,58]

CFTR-mutations: clinical presentation ?

Cystic Fibrosis Transmembran-Conductance-Regulator (CFTR) Gen-Mutation 7q31 ➔ verschiedene Formen der Pancreas-Erkrankung:

1. **klassische Cystische Fibrose** mit CF-Lungenerkrankung+ Pancreas-Insuffizienz, *aber selten klinisches Bild der Pancreatitis*:
   - erhöhte [Chlorid] im *Schweisstest* +
   - stark reduzierte CFTR-Funktion in der Nasenmucosa.

2. **pancreatitischer Phänotyp** (akute+chron.Pancreatitis) ohne Assoz. mit CF-Lungenerkrankung:
   - normale [Chlorid] im *Schweisstest* +
   - CFTR-Funktion in Nasenmucosa ist etwas reduziert aber vorhanden.

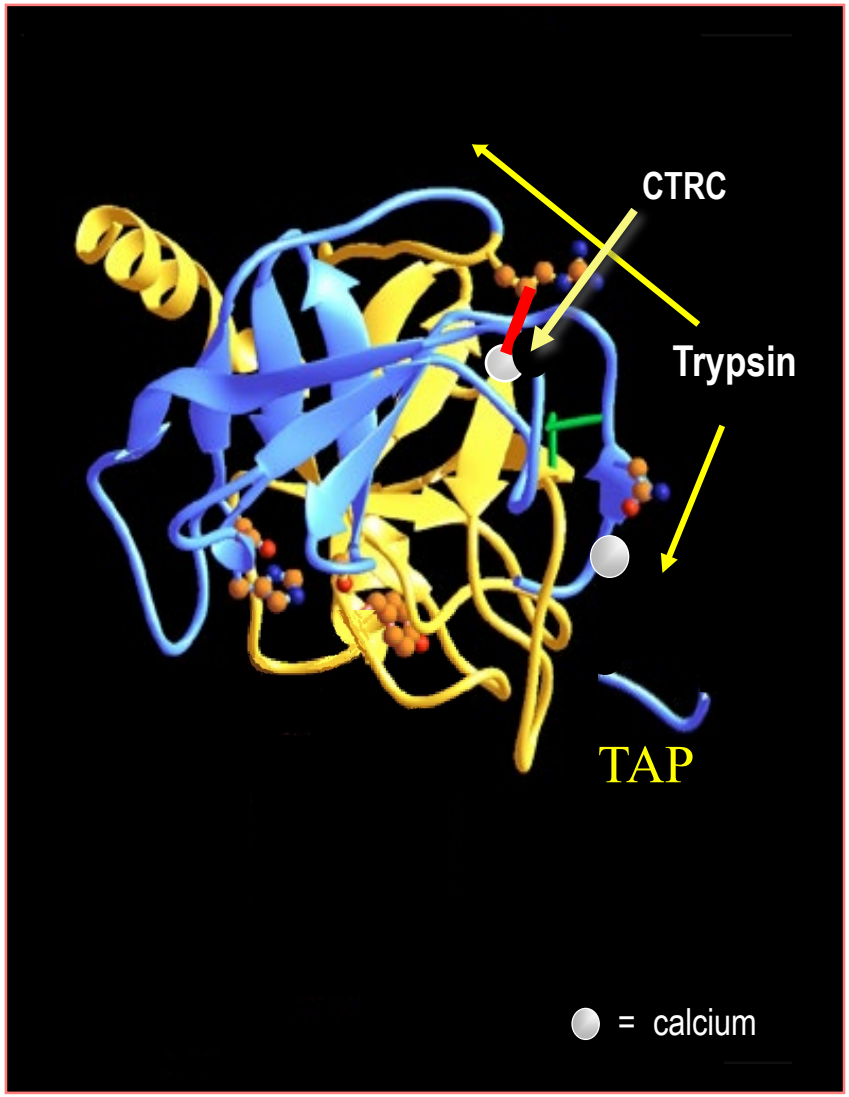
   Haben Mutation im CFTR-Gen, nicht homozygot für Mutationen die das Bild der klass. CF programmieren (Assoz. mit SPINK1 ?).

3. **heterozygote Träger der CFTR-Gen-Mutation** weisen erhöhtes Risiko einer chronischen Pancreatitis auf→ kombinierte genet. Defekte?

Trypsin(ogen) Regulation

Trypsin(ogen)

- The **master** enzyme controlling all other digestive enzymes
- Trypsinogen controlled by:
  - Trypsin(2) Calcium(2)
  - **SPINK1**



Modified from Whitcomb, Hereditary and Childhood Disorders of the Pancreas, Including Cystic Fibrosis. Sleisenger and Fordtran's Gastrointestinal and Liver Diseases, 7th Edition, 2002

Genetic Testing

- **Mendelian Disorders (HP, CF)**:
  - Testing used to confirm or establish a diagnosis in the setting of disease symptoms.
  - Genetic counseling is typically recommended prior to ordering the test, and to explain results

- **Complex Disorders: (RAP/CP syndromes)***:
  - Increases or decreases the **likelihood** that an equivocal pancreatic structural or functional test, or pancreatitis-like symptoms is a **true positive**.
  - Helps **identifies pathogenic pathways** leading to RAP, and alters the likelihood that specific complications will occur (e.g. rapid fibrosis).
  - May be useful in predictive disease modeling and personalized (individualized) medicine.

* These points reflect the personal opinion of the author and have not been agreed upon by any society or authoritative group.

- Hereditary pancreatitis (HP) is an unusual form of acute and chronic pancreatitis that runs in families. The risk of pancreatic cancer is >50 times normal.
- Although HP is only responsible for 2-3% of all cases of chronic pancreatitis, study of this disease has revolutionized our understanding of pancreatic diseases

Discovery of the Pancreatitis Gene

1. Family

Recruitment

Whitcomb 2000

2. Genetic Mapping

Hereditary Pancreatitis gene

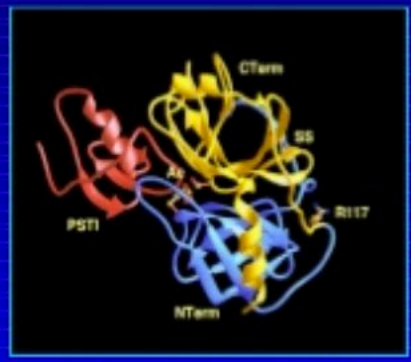
Chromosome 7

3. Mutation

ccaccaccagtcaggcac
actctaccaccATGAA
TCCACTCCTGAT
CCTTACCTTTGT
GG/ACAGCTGC
TCgtgagtatcatgccct
gcctcaggccccaaccac
ccccccgttcctggccga

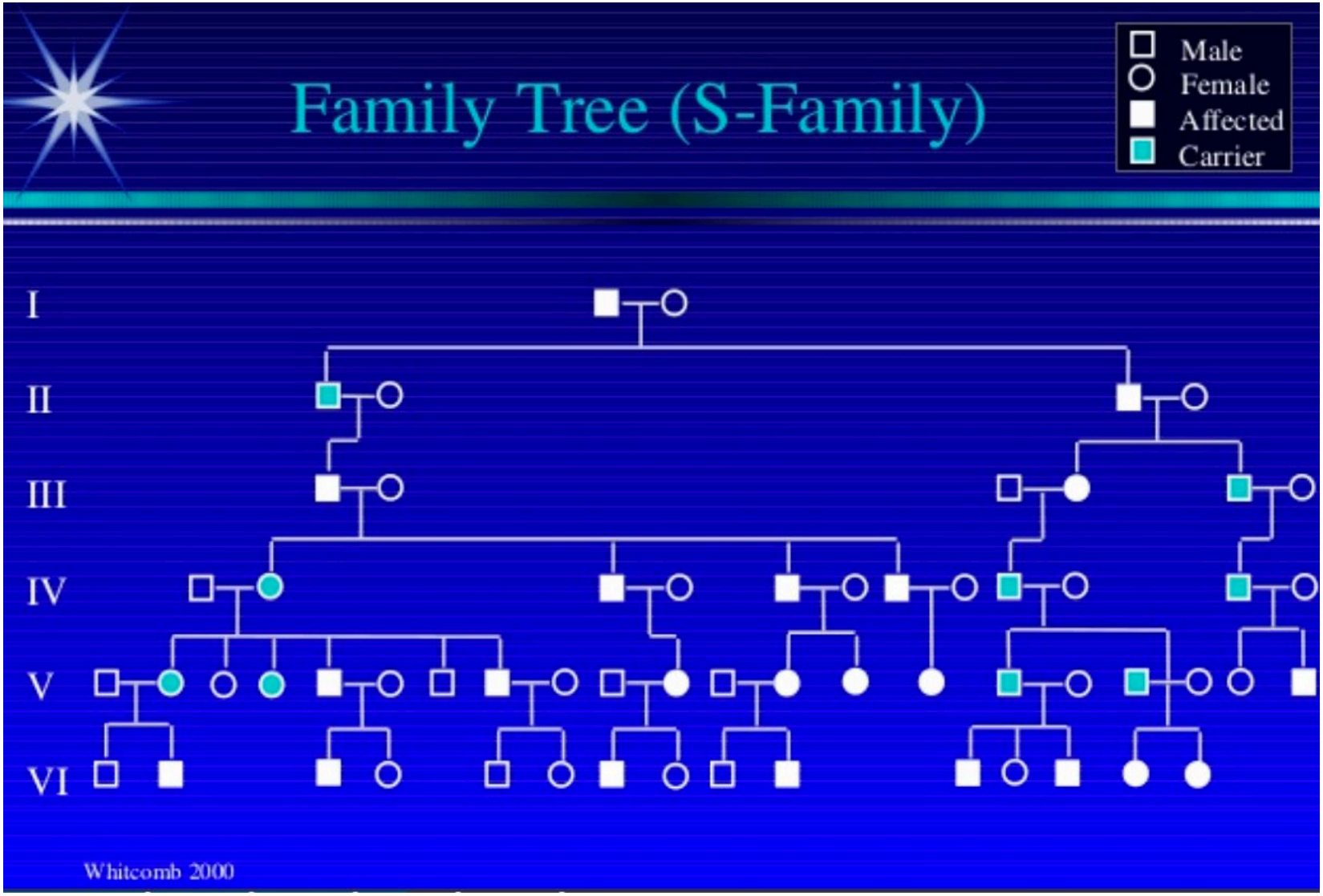
Mutation in the trypsinogen DNA sequence

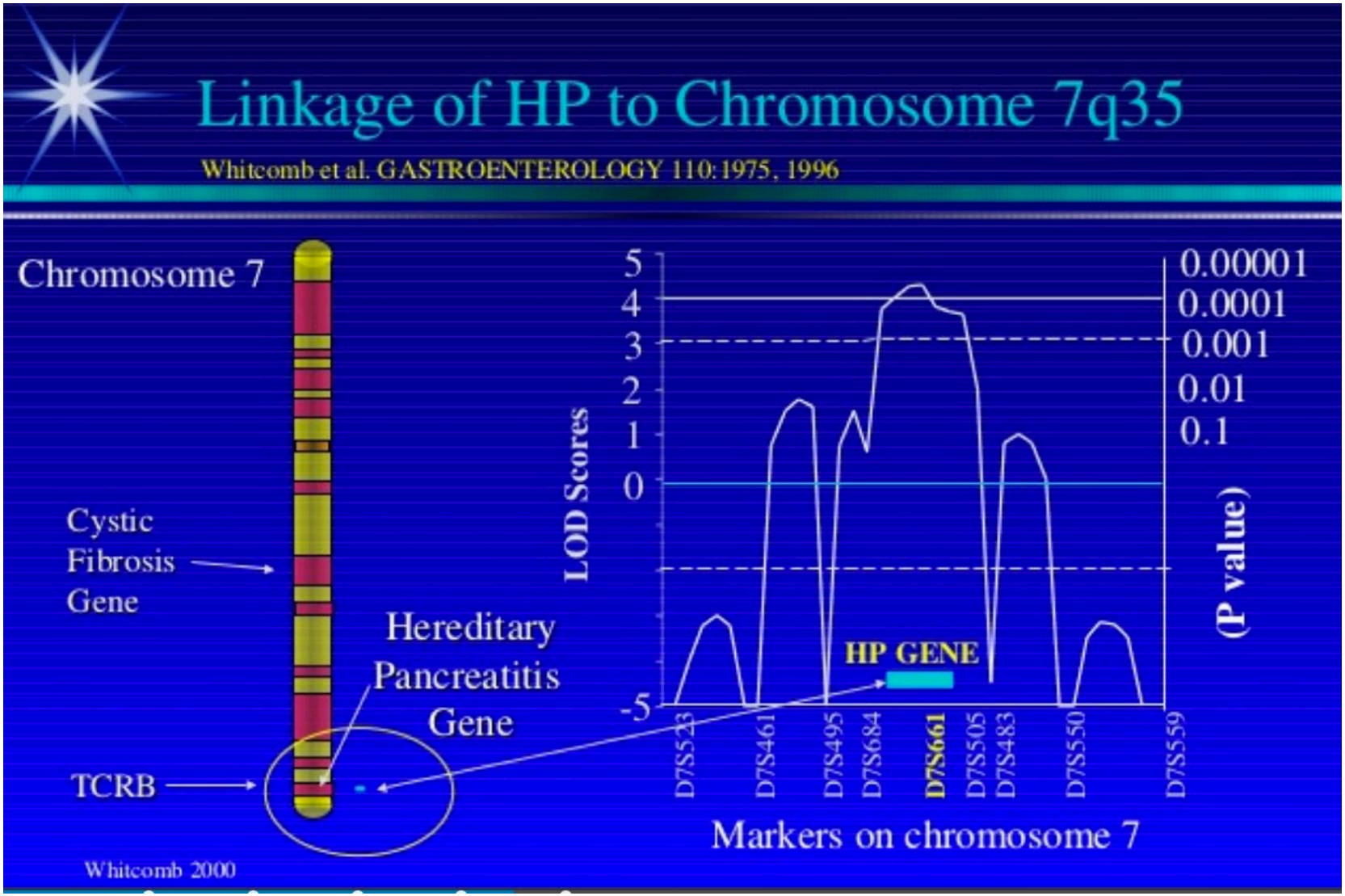
4. Mechanism



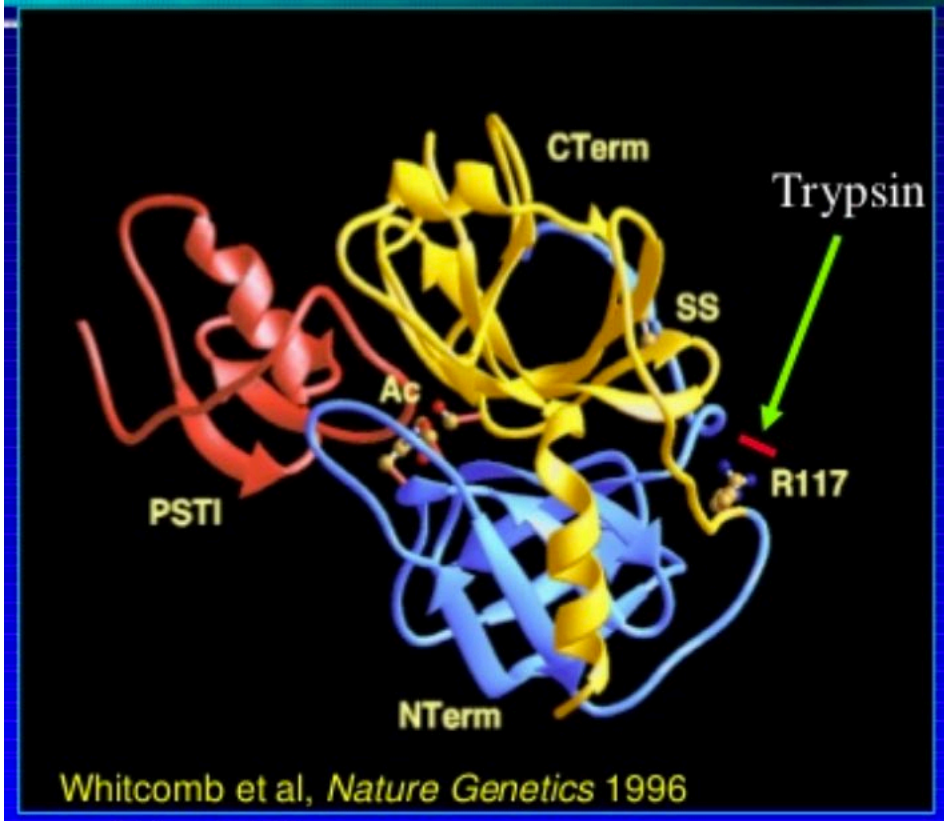
Trypsinogen

Functional significance determined


Family Tree (S-Family)
Male
Female
Affected
Carrier
I
II
III
IV
V
VI
Whitcomb 2000


Linkage of HP to Chromosome 7q35
Whitcomb et al. GASTROENTEROLOGY 110:1975, 1996
Chromosome 7
Cystic Fibrosis Gene
Hereditary Pancreatitis Gene
TCRB
Whitcomb 2000
LOD Scores
5
4
3
2
1
0
-5
0.00001
0.0001
0.001
0.01
0.1
(P value)
HP GENE
D7S513
D7S461
D7S495
D7S684
D7S661
D7S505
D7S483
D7S550
D7S559
Markers on chromosome 7

HP is caused by "Super-Trypsin"

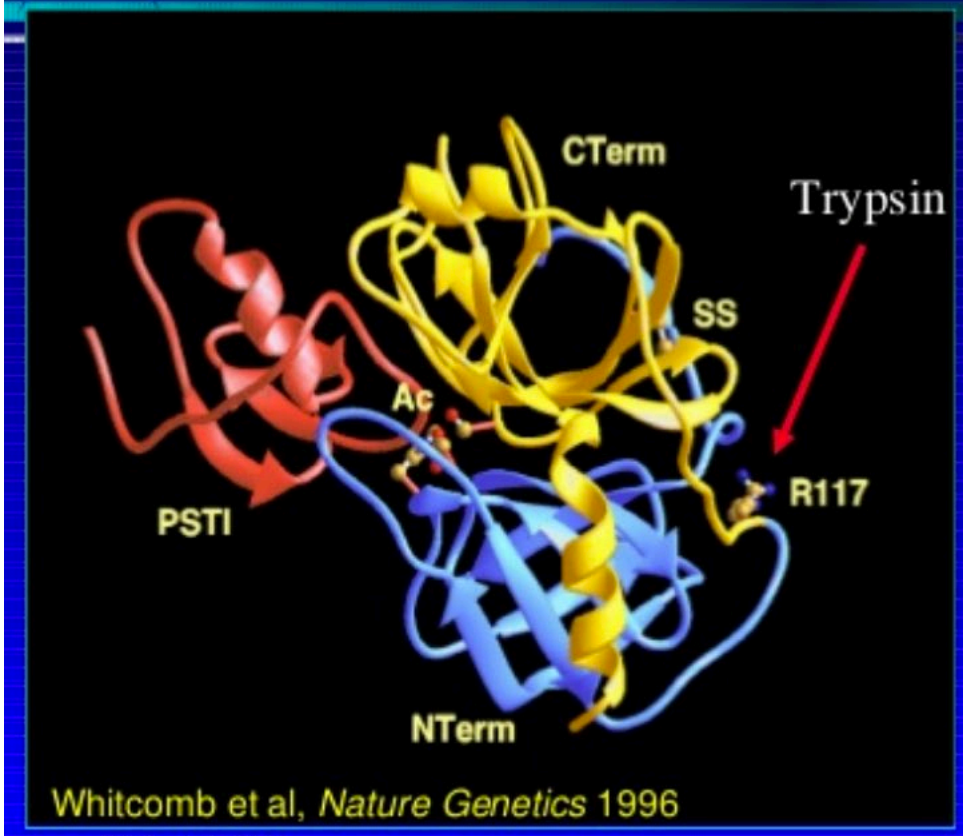


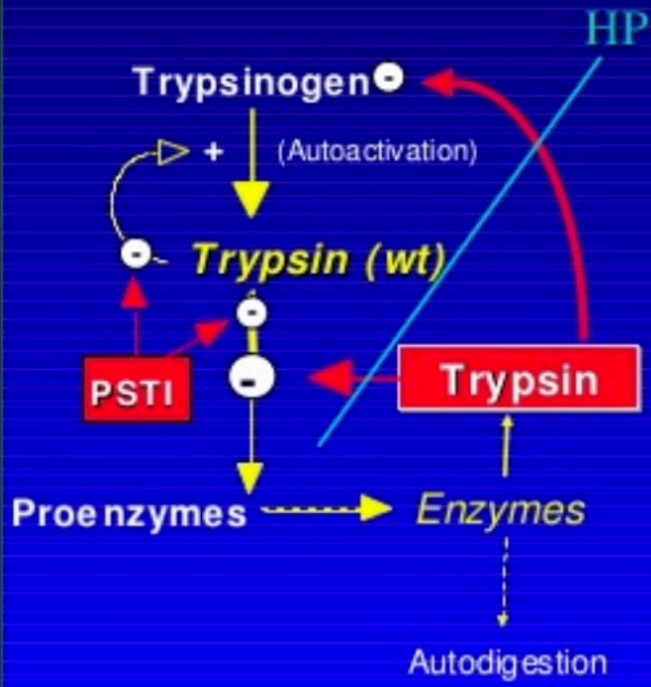
Active trypsin in the pancreas will cause the pancreas to digest itself.

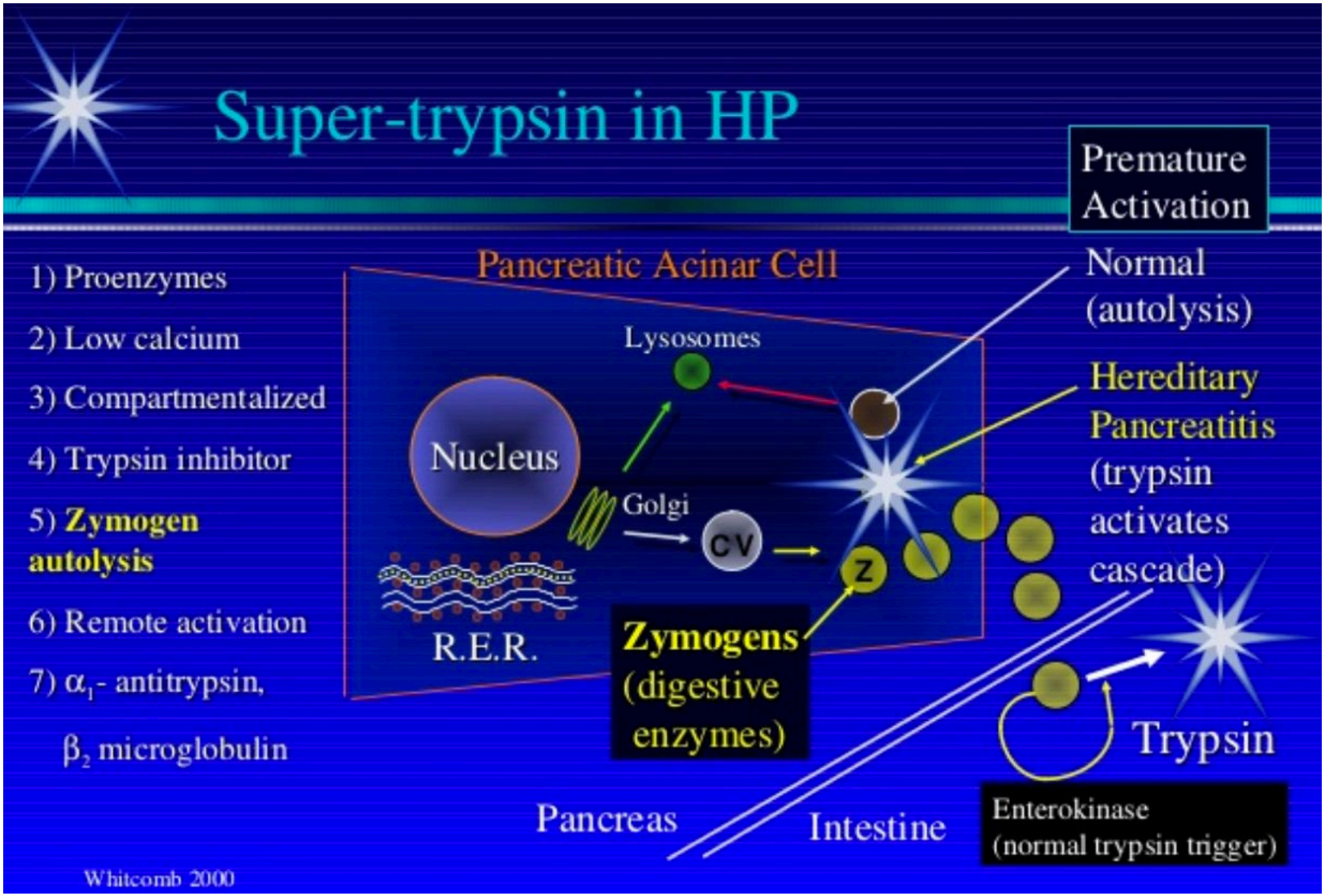
Normally, the pancreas is protected because active trypsin will destroy itself by cutting at R117. This will split the trypsin and inactivate it.

In HP, R117 is mutated to H117. This creates a "super-trypsin" that cannot be inactivated and leads to acute pancreatitis.

Fail-safe Trypsin Inactivation






Super-trypsin in HP
1) Proenzymes
2) Low calcium
3) Compartmentalized
4) Trypsin inhibitor
5) Zymogen autolysis
6) Remote activation
7) α_1- antitrypsin,
β_2 microglobulin
Pancreatic Acinar Cell
Lysosomes
Nucleus
Golgi
CV
Z
R.E.R.
Zymogens (digestive enzymes)
Premature Activation
Normal (autolysis)
Hereditary Pancreatitis (trypsin activates cascade)
Trypsin
Enterokinase (normal trypsin trigger)
Pancreas
Intestine
Whitcomb 2000

Pancreatic surveillance in germline deleterious variants of which cancer susceptability genes ?

Gene mutation	PDAC family history criteria	Agreement	Grade
LKB1/STK11 (Peutz-Jeghers syndrome)	Regardless of family history	99%	1
CDKN2A p16* (FAMMM)	With at least one affected FDR	99%	1
CDKN2A p16* (FAMMM)	Regardless of family history	77%	1
BRCA2	If at least one affected FDR, or at least two affected relatives† of any degree	93%	2
PALB2	If at least one affected FDR	83%	2
MLH1/MSH2/MSH6 (Lynch)	If at least one affected FDR	84%	2
ATM	If at least one affected FDR	88%	2
BRCA1	If at least one affected FDR	69.6%‡	3

Pancreatitis – Genetic Risk

- Pancreatitis is a **complex genetic disease**:
  - Strong underlying genetic risk of **recurrent acute** pancreatic injury (susceptibility).
  - Strong underlying genetic risk of progression to **fibrosis, pain, diabetes, cancer**. (disease modifiers)
  - Environmental factors such as **alcohol** and **smoking** **accelerate** and **worsen** pancreatic disease
- Early knowledge of the **basis of increased risk** could be used to improve diagnostic certainty, identify syndromes and target therapy.
- Genetics is predicted to **change pancreatic disease management** from *treating end-stage symptoms* to **minimizing the disease!**

Hilfreiche Tricks – im Zweifelsfall

- Im Zweifelsfall hilfreiche Tricks
  MR mit Diffusion:
  Papillenbiopsie: IgG4+
  EUS mit Elastographie / KM ?
  ERCP: s. o.

Is biliary drainage needed in obstructive jaundice before treatment ?

- "Biliary drainage is useful to prevent biliary infection and use of brushing and cytology can differentiate IgG4-SC from biliary malignancy." (level B).
- "In some cases of mild jaundice without signs of infection, steroid treatment alone can be performed safely without biliary stenting." (level B).

AIP Evaluation and Treatment

- Start **prednisone 40 mg/day** for 4 weeks.
- After 4 weeks, assess response by clinical evaluation, radiology, and serology (IgG4 levels).
- If clinical, serologic, or radiographic response was documented (and **dramatic**), then
  - Taper prednisone 5 mg/wk until gone.
- If limited response, consider biopsy and/or **cancer** evaluation.
- If AIP documented and recurrent, then consider adding immunosuppression (e.g. azathioprine)

Typen Autoimmun-Pankreatitis

	Typ I (LPSP) Lymphoplasm. Skleros. Pankreatitis	Typ II (IDCP) Idiopath.ductozentr. Pankreatitis
Epidemiologie	Ca. 60% der AIP M:W = 3:1 6. Lebensdekade	Ca. 40 % der AIP M:W = 1:1 4./5. Lebensdekade
Klinik	Ikterus 75% Akute Pankreatitis 5% Fremdorganmanifestationen (z.b. AIC, Sialadenitis etc.) da **IgG4-**assoziierte Erkrankung	Ikterus 50% Akute Pankreatitis 33% CED (v.a. CU) assoziie Sonst keine system. Manifestation
Labor	**IgG4**-Titer erhöht Erhöhte ANA-, RF, Gamma-Glob.	IgG4 normwertig Kaum veränderte Cher
Histologie	**IgG4+** ICH (> 10/ HPF)	Keine IgG4+Zellen
Prognose	Bis 50% Rezidive, v.a. bei system. Manifestation/en	Kaum Rezidive

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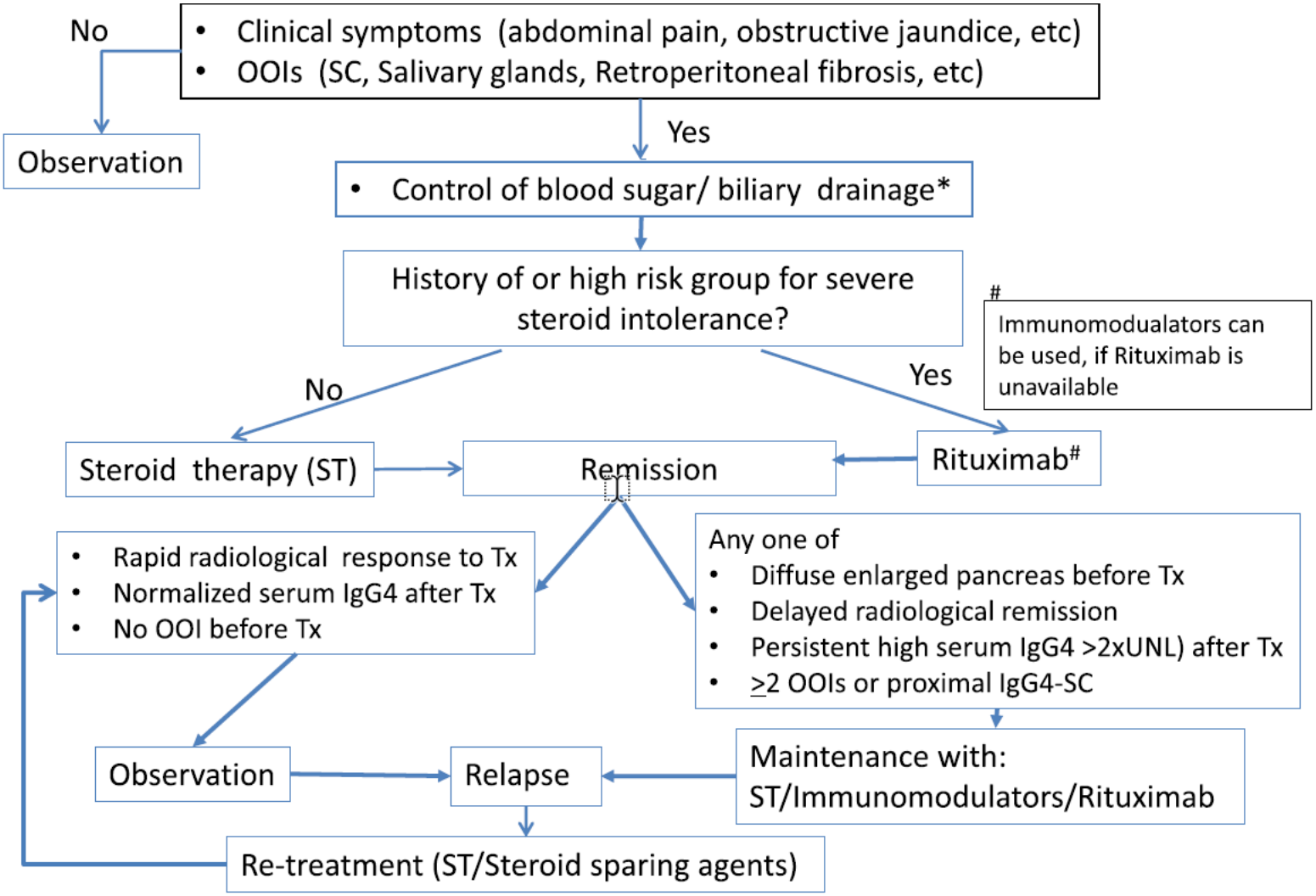

No
• Clinical symptoms (abdominal pain, obstructive jaundice, etc)
• OOIs (SC, Salivary glands, Retroperitoneal fibrosis, etc)
Observation
Yes
• Control of blood sugar/ biliary drainage*
History of or high risk group for severe steroid intolerance?
#
Immunomodualators can be used, if Rituximab is unavailable
No
Yes
Steroid therapy (ST)
Remission
Rituximab#
• Rapid radiological response to Tx
• Normalized serum IgG4 after Tx
• No OOI before Tx
Any one of
• Diffuse enlarged pancreas before Tx
• Delayed radiological remission
• Persistent high serum IgG4 >2xUNL) after Tx
• ≥2 OOIs or proximal IgG4-SC
Observation
Relapse
Maintenance with: ST/Immunomodulators/Rituximab
Re-treatment (ST/Steroid sparing agents)

TypI: Autoimmun-Pankreatitis

Kriterium	Level 1	Level 2
P *Parenchym Bildgebung*	Typisch Diffus vergößert mit late enhancement (manchmal kapselartige Randverstärkung)	Unklar Herdförmig/fokale vergrößert mit late enhancement
D *Duktale Bildgebung ERP*	Lange (> 1/3 des Verlaufs) oder multiple Striktu-ren des Pankreasgangs ohne proximale Dilatation	Segmentale/fokale Strikturen mit proximaler Dilatation bis 5 mm
S *Serologie*	IgG4 > 2-fach erhöht	IgG4 1-bis 2-fach erhöht
OOI *Andere betroffene Organe* *(other organ involvement)*	**a)** oder **b)** müssen zutreffen **a)** mindestens 3 der folgenden histologischen Hinweise in anderem Organen: ▸ Lymphoplasmazelluläres Infiltrat und Fibrose ohne Granulozyten ▸ Storiforme Fibrose ▸ Obliterierende Phlebitis ▸ IgG4-positiven Plasmazellen (> 10/ Gesichtfeld) **b)** mindestens einer der folgenden radiologische Hinweise: ▸ Segmentale/multiple proximale Gallengangstrikturen ▸ Retroperitoneale Fibrose	**a)** oder **b)** müssen zutreffen **a)** beide histologischen Kriterien ande-rer Organe inklusive des Gallengangs müssen erfüllt sein: ▸ Lymphoplasmarzelluläres Infiltrat ohne Granulozyten ▸ IgG4-positiven Plasmazellen (> 10 pro Gesichtfeld) **b)** Nachweis mindestens eines der folgenden Kriterien aus radiologischer oder körperlicher Untersuchung: ▸ Symmetrisch vergößerte Speicheldrüsen ▸ Einbeziehung der Nieren
H *Histologie Pankreas*	3 von 4 LPSP-Kriterien (**Tab. 6**) in TruCut-Biopsat oder Resektat	2 von 4 LPSP-Kriterien (**Tab. 6**) in TruCut-Biopsat oder Resektat
Rt *Erfolg der Steroidtherapie*	Schnelles Ansprechen (≤ 2 Wochen) auf einen Therapieversuch mit radiologischem Nachweis einer deutlichen Besserung	

Typ-II: Autoimmune-Pancreatitis

Kriterium	Level 1	Level 2
P *Parenchym-Bildgebung*	Typisch Diffus vergößert mit late enhancement (manchmal kapselartige Randverstärkung)	Unklar bis atypisch* Herdförmig/fokal vergrößert mit late enhancement
D *Duktale Bildgebung ERP*	Lange (> 1/3 des Verlaufs) oder multiple Striktu-ren des Pankreasgangs ohne proximale Dilatation	Segmentale/fokale Strikturen mit proximaler Dilatation bis 5 mm
OOI *andere Organe*		Klinische Diagnose einer chronisch entzündlichen Darmerkrankung
H *Histologie Pankreas*	Beide Kriterien ▸ GEL mit oder ohne granulozytärem Azinusinfiltrat ▸ Abwesenheit oder wenige (> 10 pro Gesichtsfeld) IgG4-positive Plasmazellen	Beide Kriterien ▸ Granulozytäres und lymphoplasma-tisches Azinusinfiltrat ▸ Keine oder wenige (> 10 pro Gesichts-feld) IgG4-positive Plasmazellen
Rt *Erfolg der Steroidtherapie*	Schnelles Ansprechen (≤ 2 Wochen) auf einen Therapieversuch mit radiologischem Nachweis einer Heilung oder deutlichen Besserung	

	Bildgebung	weitere
Definitiv	Typisch/unklar	Histologisch gesicherte IDCP (Level 1 H) oder CED + Level 2 H + Rt
Wahrscheinlich	Typisch/unklar	Level 2 H/ CED + Rt

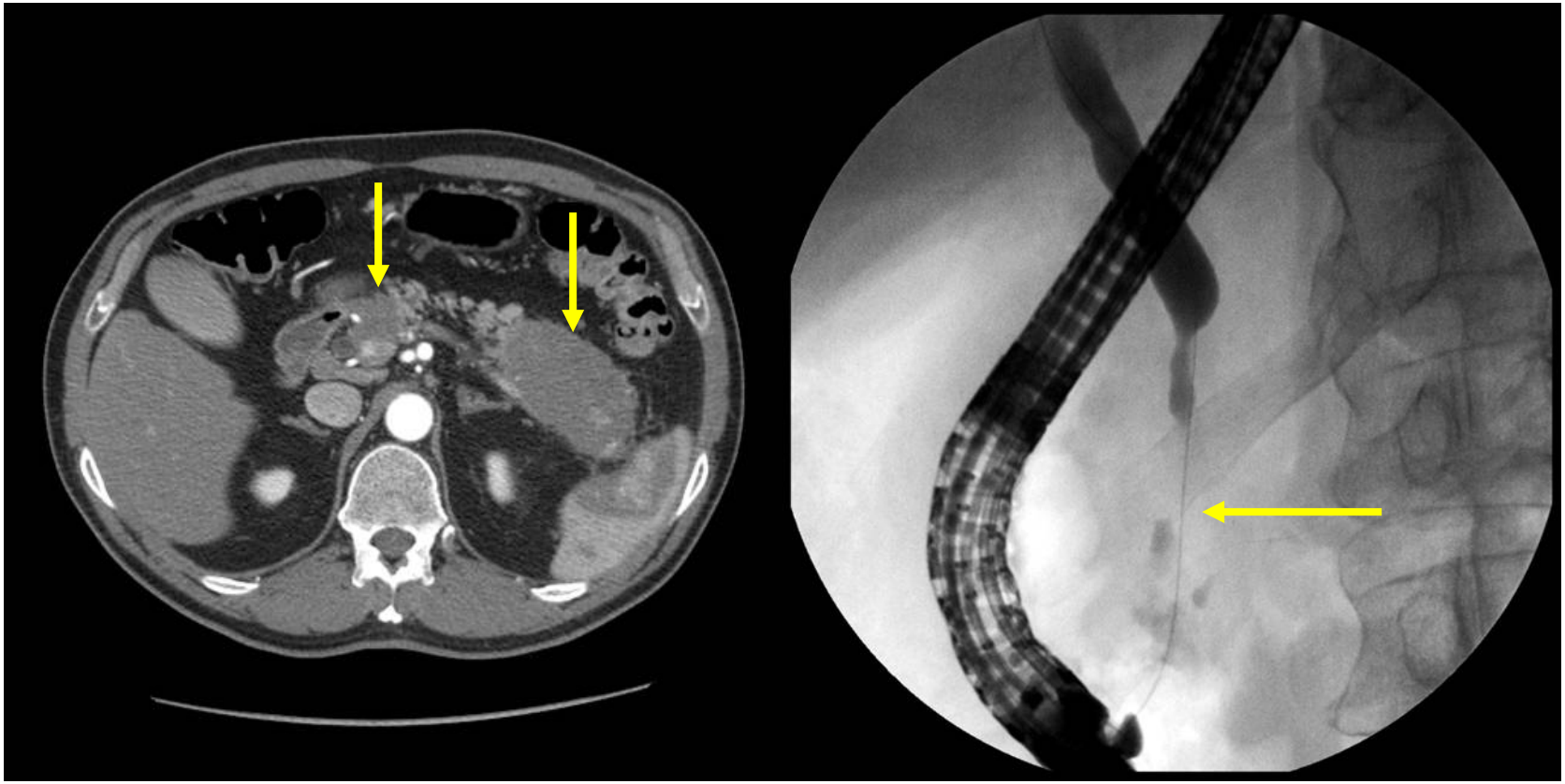
Autoimmune Pancreatitis Case

59 yr retired coal miner, presents with 2 week history of painless jaundice, dark urine, and 16 lb weight loss.

Past History: Diabetes for 8 years (uncontrolled in past few months), Osteoarthritis
Family History: Unremarkable
Social History: Does not drink or smoke
Medications: Insulin, occasional analgesics
Physical Exam: Icteric sclera, enlarged submandibular glands, otherwise normal.
Labs: Total bilirubin - 4.2, Direct bilirubin - 3.1,
ALT - 306, AST - 140, ALP - 264, CA 19-9 - normal

From Dhiraj Yadav MD MPH

Type 1 AIP



FNA cytology: negative for malignant cells

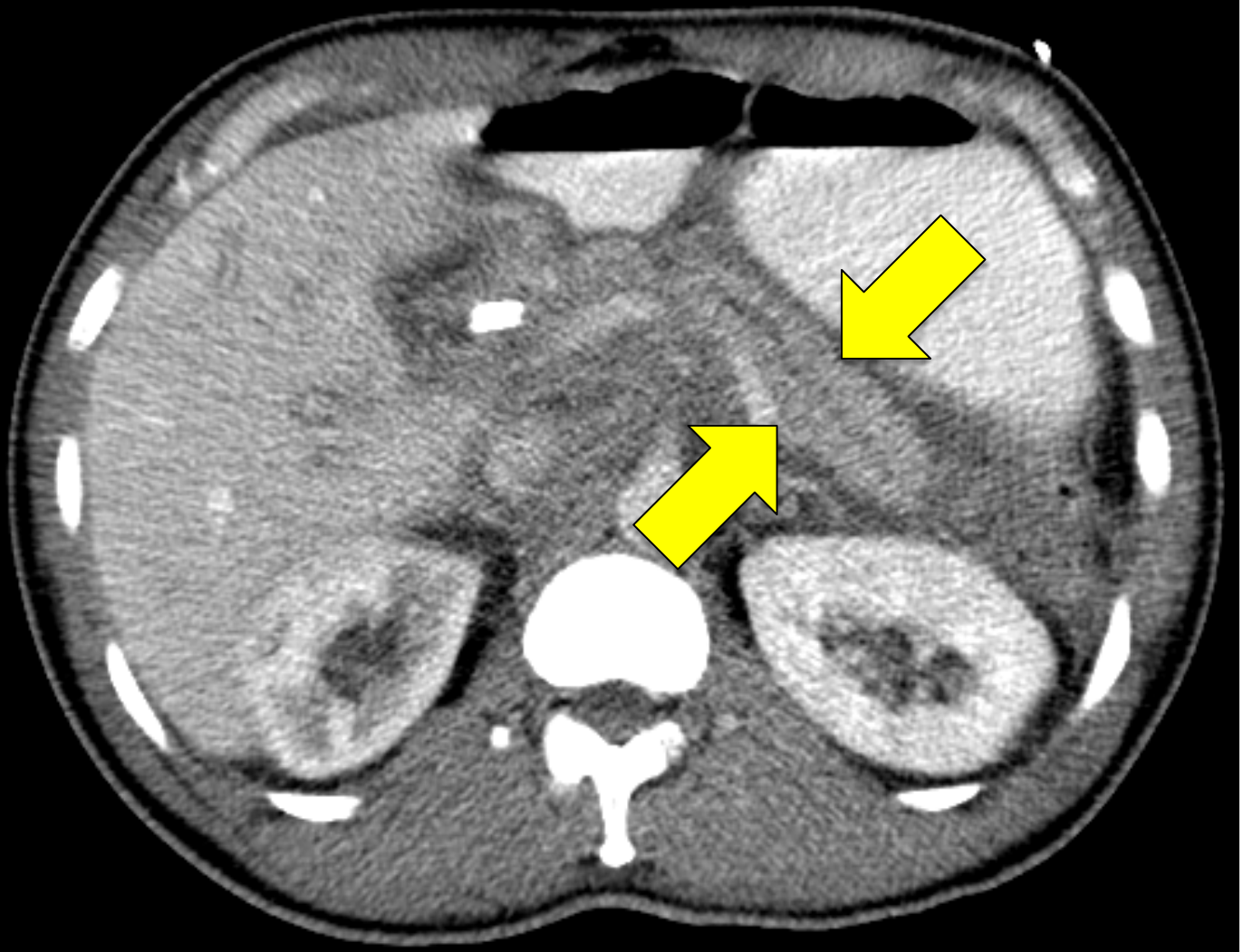
Pancreasfest 2009

Follow up

- Initial improvement on steroids
- Developed extrapancreatic biliary strictures
- ERCP with stents.
- Added azathioprine, not tolerated
- Treated with Mycophenolate Mofetil (CellCept)– resolution of strictures, stents removed

From Dhiraj Yadav MD MPH

45 year old man with acute pancreatitis and PEI that did not reso



Serum IgG4 was normal: EUS FNA demonstrated lymphoma.

Pancreatic Genetics

Mendelian genetics

Complex genetics

Genetic tests and interpretation

INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HOPITAL UNIVERSITAIRE DE BERNE
BERN UNIVERSITY HOSPITAL

Hereditäre „familiäre“ Pancreatitis

- autosomal dominant
- Penetranz 80%
- +FA: Pancreatitis-Schübe ab Kindheit
  Progression zur chronischen Pancreatitis
- forcierte *Progression der CP durch Alkohol-Konsum.*
- Mutation (7q35) im kationischen Trypsinogen-Gen (**PRSS1**).

- entdeckt 1996,
- bekannt sind
  > 25 Mutationen

- Häufigste Mutation(Arg122His) mit Defekt Arg117:
  ➔krankmachende **Resistenz gegen proteolyt. Trypsin-Abbau**
- Hohes *(35x) Pancreas-Carcinom-Risiko: 50J: 10%; 75J: 50%*

[Comfort MW. Gastro1952;21:54-63; FelderbauerP. Digestion2008;78:60-5; Rebours V. AJG2008;103:111-9]