

Can Serology Supplant Endoscopy Biopsy for Diagnosis and Monitoring of Celiac Disease?

Alessio Fasano, M.D.

Mucosal Biology Research Center
University of Maryland School of Medicine

Pathogenesis



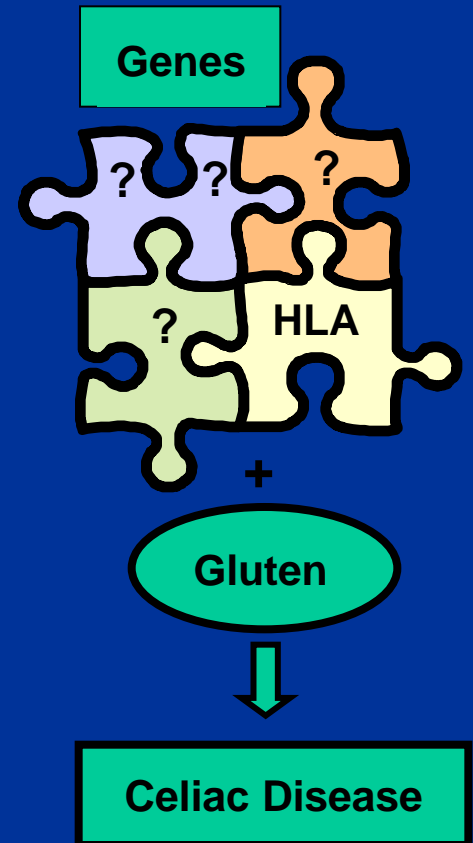
- Genetic predisposition
- Environmental triggers
 - Dietary
 - Non dietary?





Genetics

- Several genes are involved
- The most consistent genetic component depends on the presence of HLA-DQ (DQ2 and / or DQ8) genes
- Other genes (not yet identified) account for 60 % of the inherited component of the disease
- HLA-DQ2 and / or DQ8 genes are necessary (No DQ2/8, no Celiac Disease!) but not sufficient for the development of the disease





Be aware DR3 should now be referred to as DR17

DQ2 {
DQA1*0501
DQA1*0201
DQB1*0201

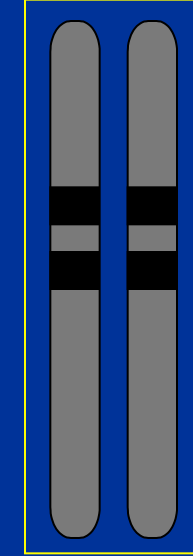
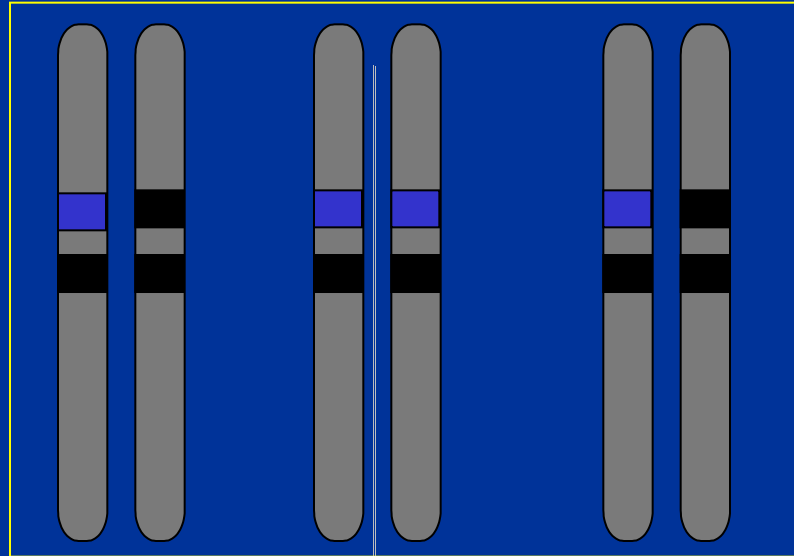
DQ2

DQ8

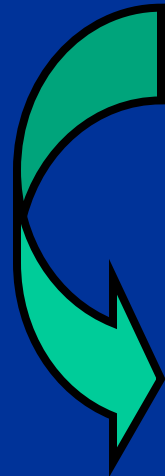
DR3

DR3/DR3

DR5/DR7



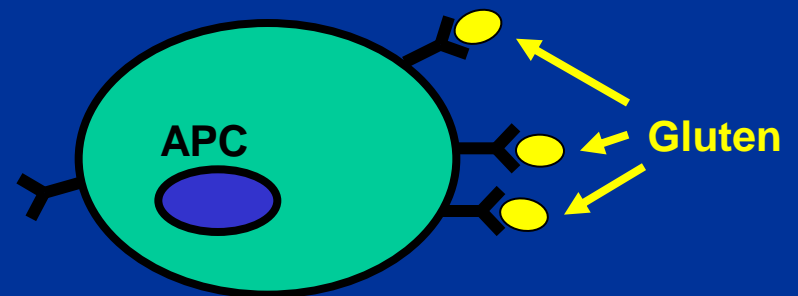
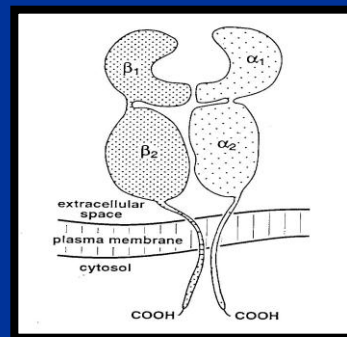
DQA: Any
DQB1*03



CIS

CIS

Trans



Diagnosis

Diagnostic principles

- Confirm diagnosis before treating
 - Diagnosis of Celiac Disease mandates a strict gluten-free diet for life
 - following the diet is not easy
 - Commitment for life
 - QOL implications
- Failure to treat has potential long term adverse health consequences
 - increased morbidity and mortality



Serological Tests

Role of serological tests:

- Identify symptomatic individuals who need a biopsy
- Screening of asymptomatic “at risk” individuals
- Supportive evidence for the diagnosis
- Monitoring dietary compliance



Serological Tests

- Antigliadin antibodies (AGA)
- Antiendomysial antibodies (EMA)
- Anti tissue transglutaminase antibodies (TTG)
 - first generation (guinea pig protein, not used anymore)
 - second generation (human recombinant)
- Anti Actin Antibodies (AAA)
- HLA typing



Antigliadin Antibodies

- Antibodies (IgG and IgA) to the gluten protein in wheat, rye and barley
- Advantages
 - relatively cheap & easy to perform
- Disadvantages
 - poor sensitivity and specificity (cannot distinguish between the autoimmune process typical of celiac disease and gluten allergy/sensitivity).



Endomysial Antibody - EMA

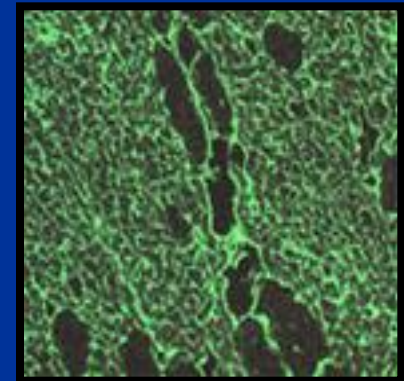
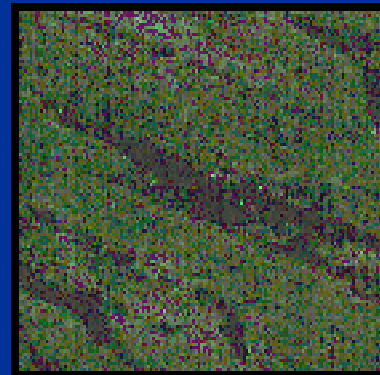
- IgA based antibody against reticulin connective tissue around smooth muscle fibers
- Advantages
 - high sensitivity and specificity
- Disadvantages
 - false negative in young children
 - operator dependent
 - expensive & time consuming
 - false negative in IgA deficiency



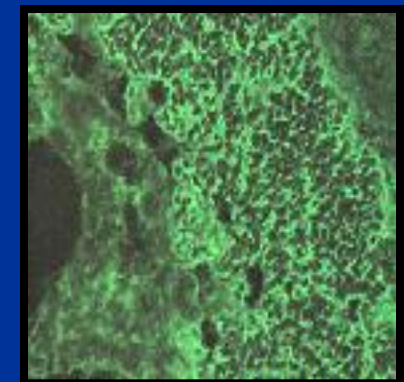
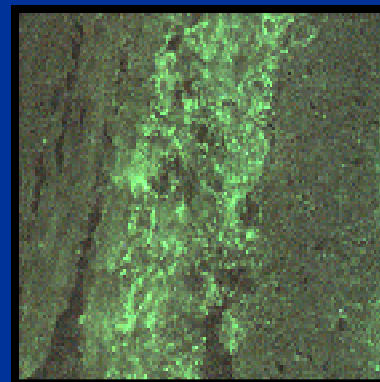
Endomysial Antibody - EMA

NEGATIVE

POSITIVE



Antibodies against the outer layer of the smooth muscle of monkey esophagus



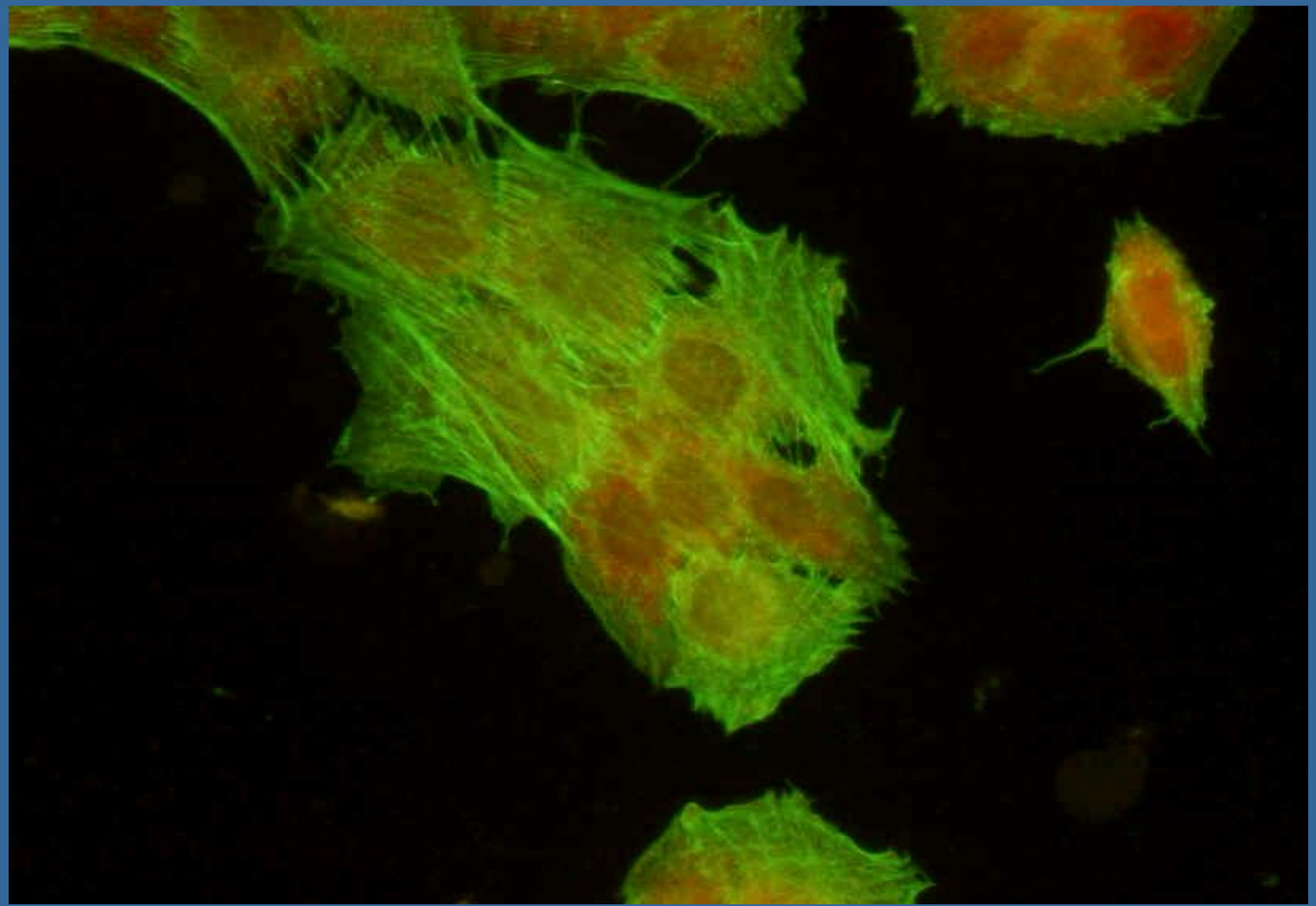
Tissue Transglutaminase - TTG

- IgA based antibody against tissue transglutaminase (Celiac Disease autoantigen)
- Advantages
 - high sensitivity and specificity (human TTG)
 - non operator dependent (ELISA/RIA)
 - relatively cheap
- Disadvantages
 - false negative in young children
 - false negative in IgA deficiency
 - possibly less specific than EMA

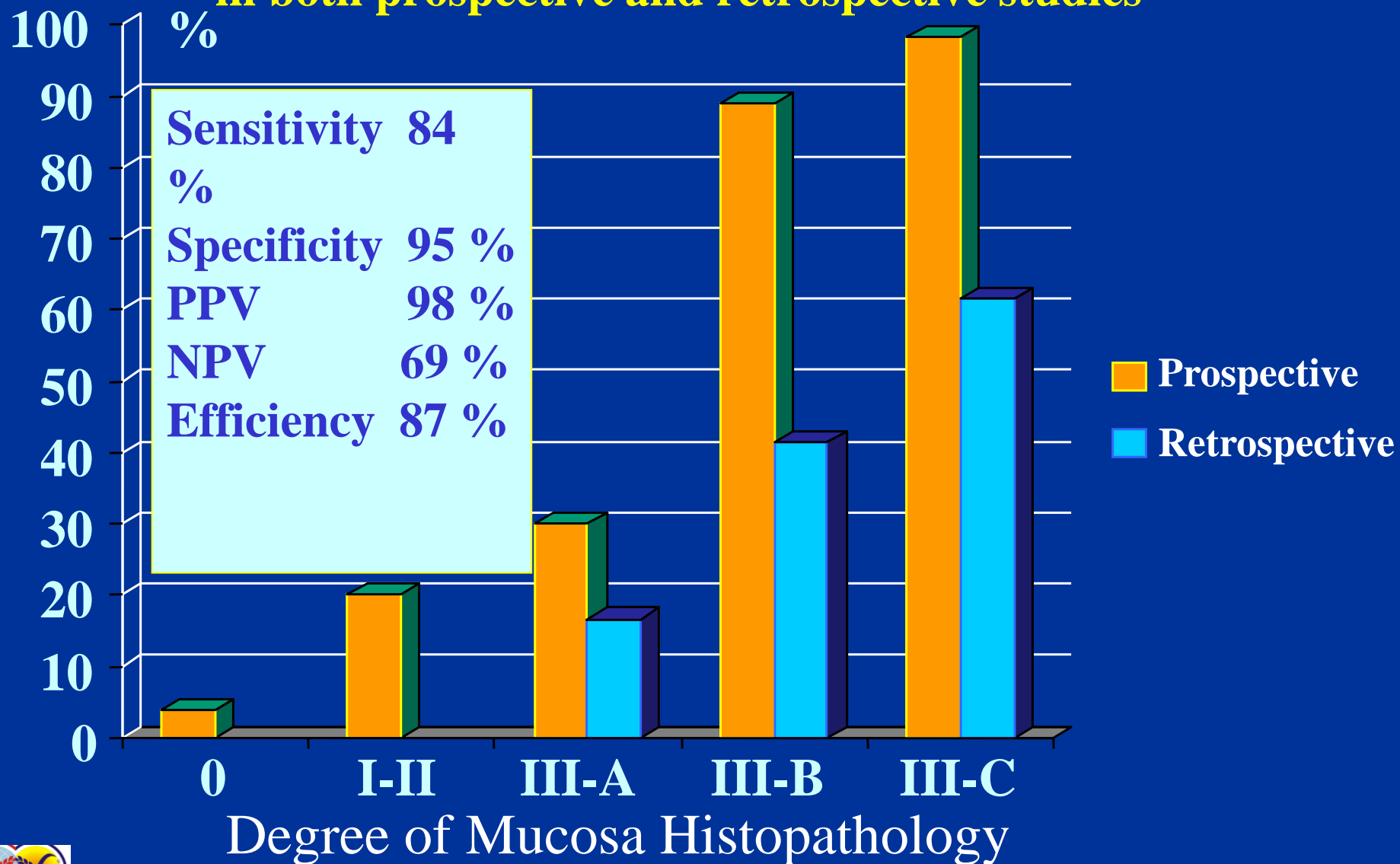


Anti-Actin Antibodies:

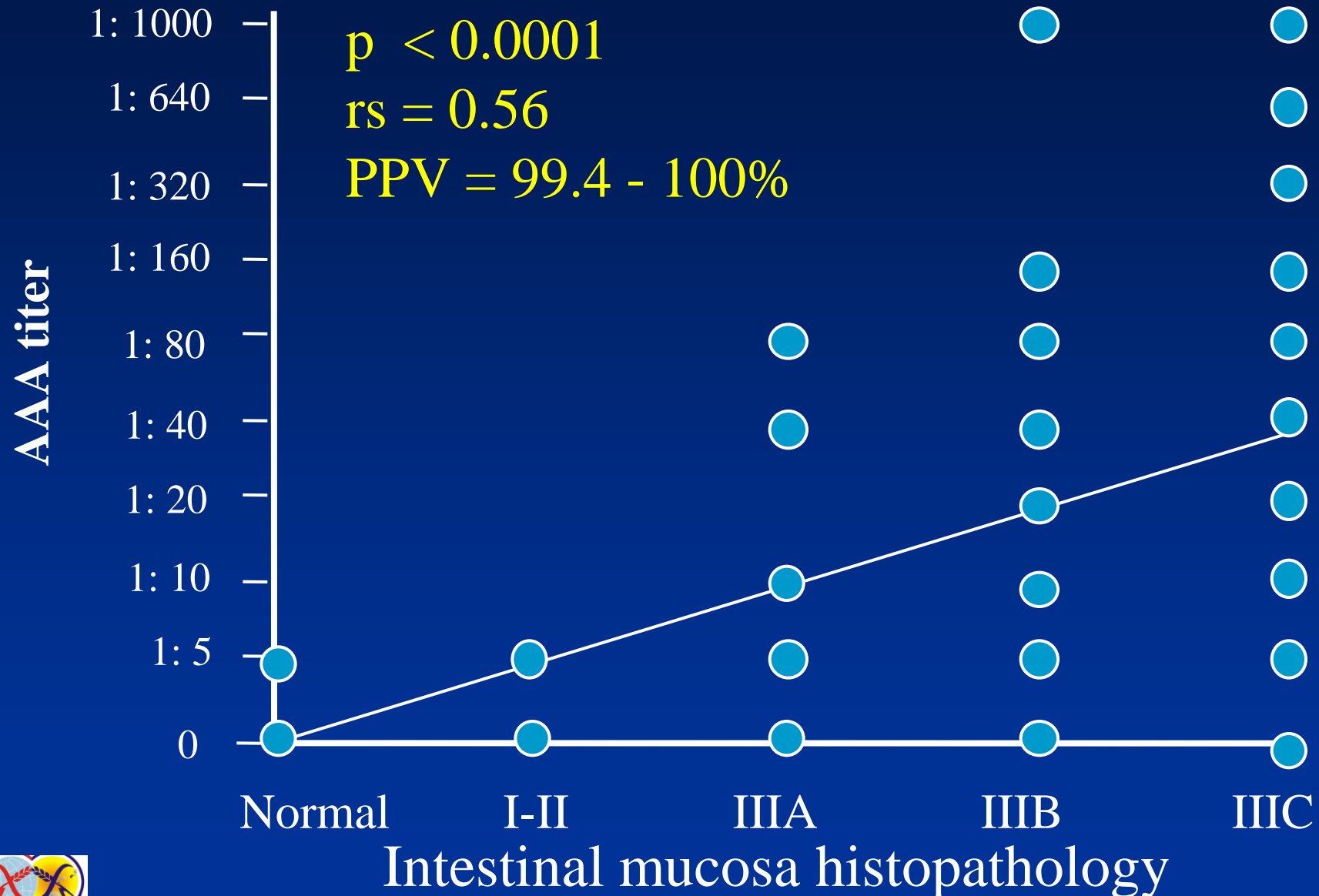
Fluorescence microscopy image of colchicine-treated intestinal epithelial cells (IEC-6)



Percent of IgA-AAA positive celiac patients and biopsied controls subdivided according to the degree of mucosa histopathology in both prospective and retrospective studies



Correlation between IgA-AAA serum titer and intestinal mucosa morphology (bivariate scattergram with regression)



Which subjects will benefit from this new test ?

Any AEA and/or TGA positive patient whether:

1 - **the biopsy is difficult to interpret:**

- patchy distribution of intestinal villous atrophy not picked up by the biopsy
- artifact damage of specimens not adequately handled

2 - **the biopsy represents a life-threatening risk:**

- any contraindication to procedures
- pregnant women with a history of multiple pregnancy losses
- subjects with coagulation disorders.



Serological Test Comparison

	Sensitivity %	Specificity %
AGA-IgG	69 – 85	73 – 90
AGA-IgA	75 – 90	82 – 95
EMA (IgA)	85 – 98	97 – 100
TTG (IgA)	90 – 98	94 – 97
AAA (IgA)	80 – 85	92 - 95

Modified from Farrell RJ, and Kelly CP. Am J Gastroenterol 2001;96:3237-46.



HLA Tests

HLA alleles associated with Celiac Disease

- DQ2 found in 95% of celiac patients
- DQ8 found in remaining patients
- DQ2 found in ~30% of general population

Value of HLA testing

- High negative predictive value
 - Negativity for DQ2/DQ8 excludes diagnosis of Celiac Disease with 99% confidence



HLA Tests

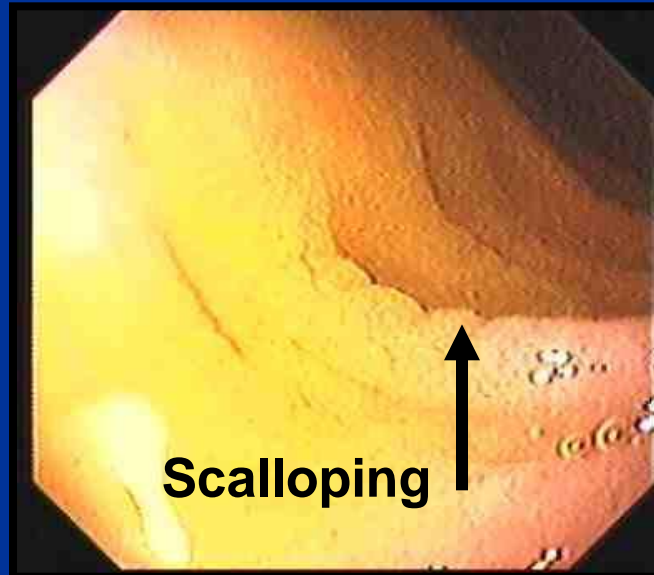
- Potential role for DQ2/DQ8
 - asymptomatic relatives
 - Down, Turner & Williams syndrome
 - type 1 diabetes
 - diagnostic dilemmas



Endoscopic Findings



Normal Appearing



Scalloping

Scalloping

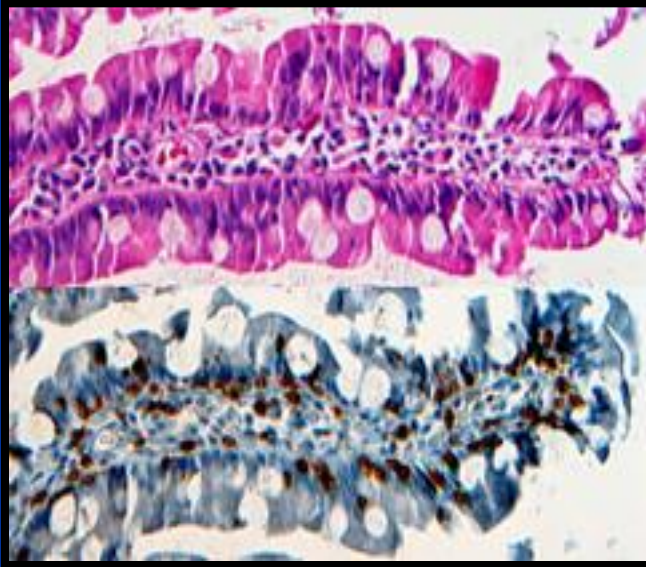


Nodularity

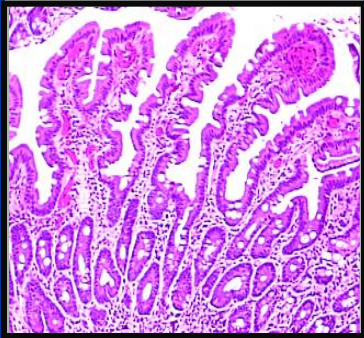


Biopsy Diagnosis

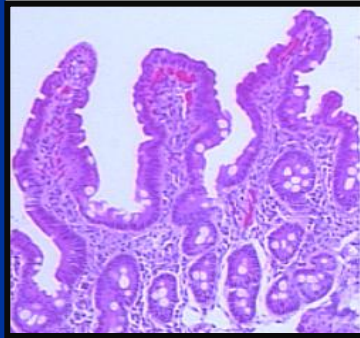
- Histologic Features:
 - Increased IEL's ($> 30/100$ enterocytes)
 - Loss of nuclear polarity
 - Change from columnar to cuboid
 - Lamina propria cellular infiltrate
 - Crypt elongation and hyperplasia
 - Increased crypt mitotic index
 - Progressive villous flattening



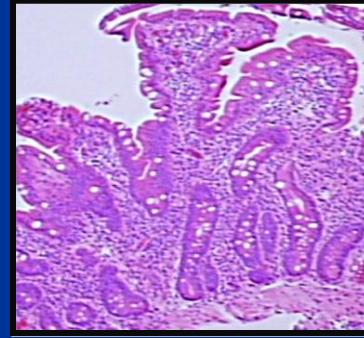
Histological Features



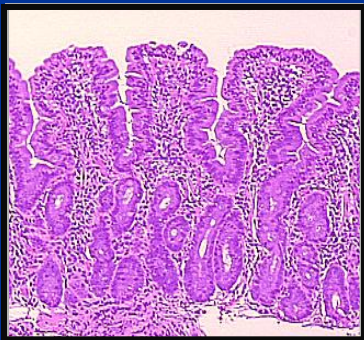
Normal 0



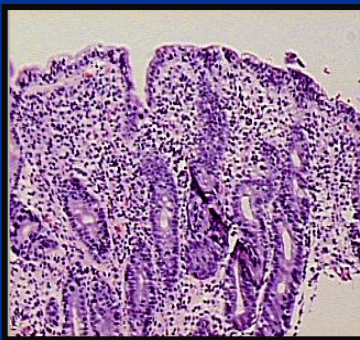
Infiltrative 1



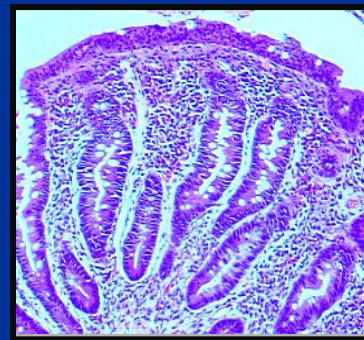
Hyperplastic 2



Partial atrophy 3a



Subtotal atrophy 3b

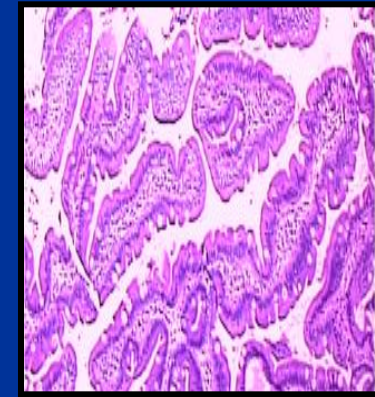
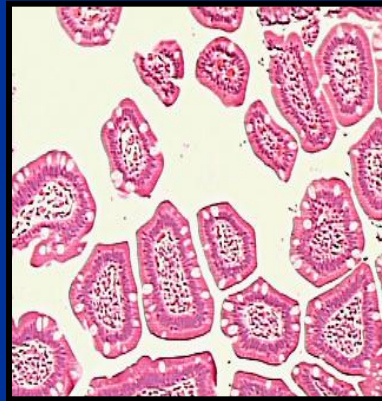
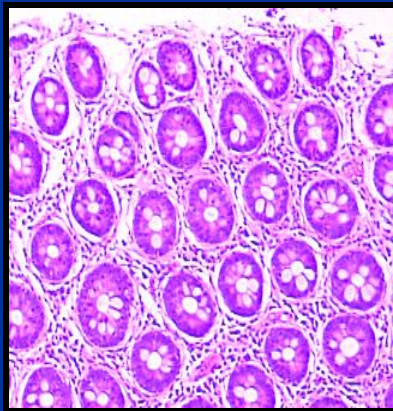
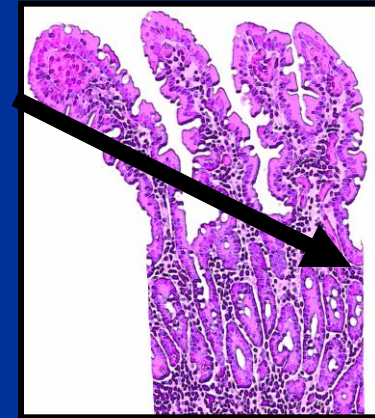
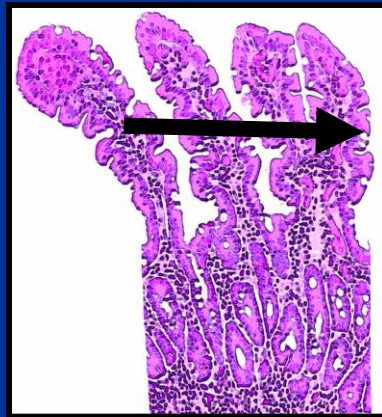


Total atrophy 3c



Diagnostic Pitfalls

Poor Orientation



Fantastic Voyage: Capsule endoscopy



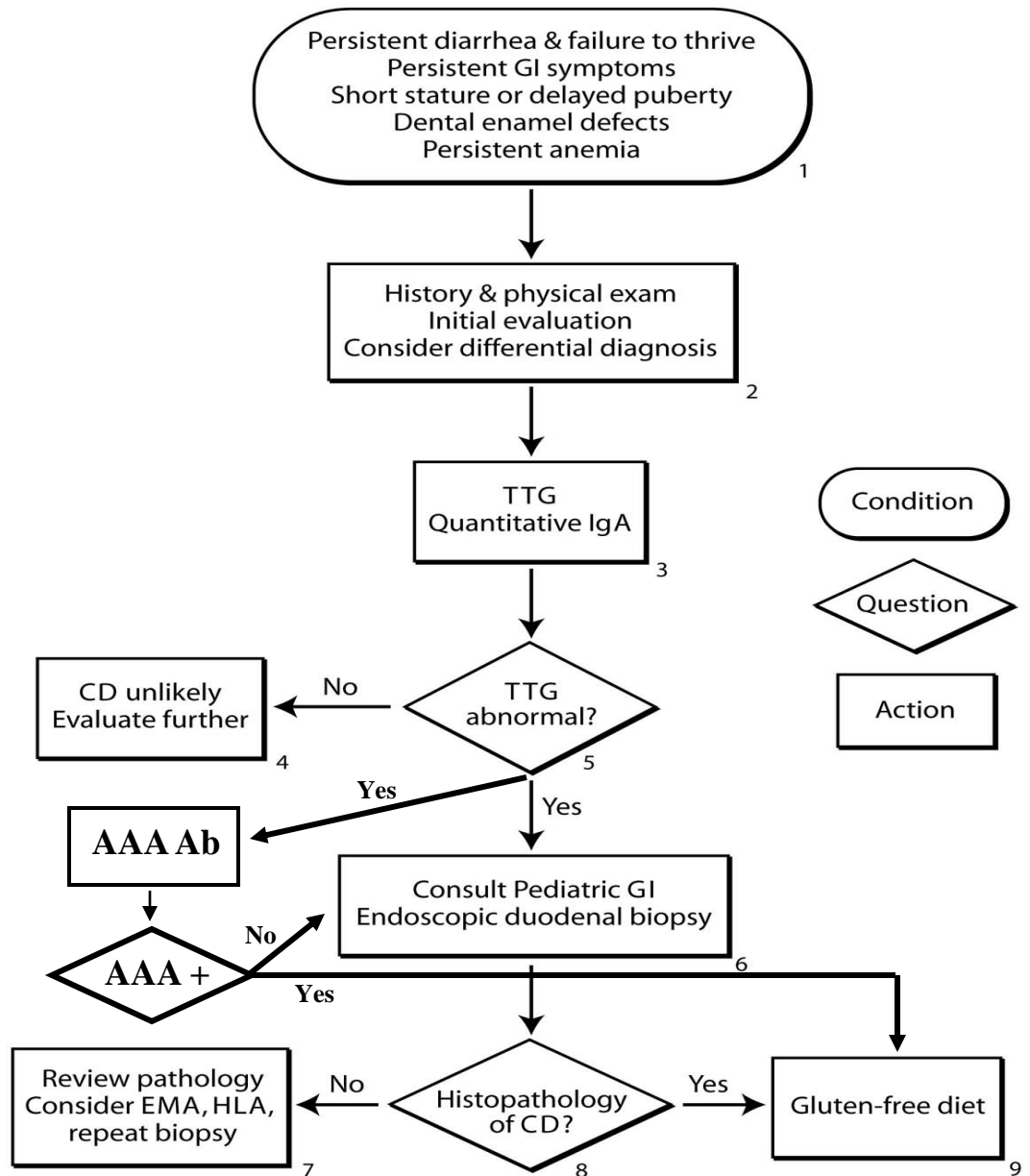
Celiac



Normal



Diagnostic Algorithm



Hill I.D. et al *J Ped Gastroenterol Nutr* 2005; 40:1-19

