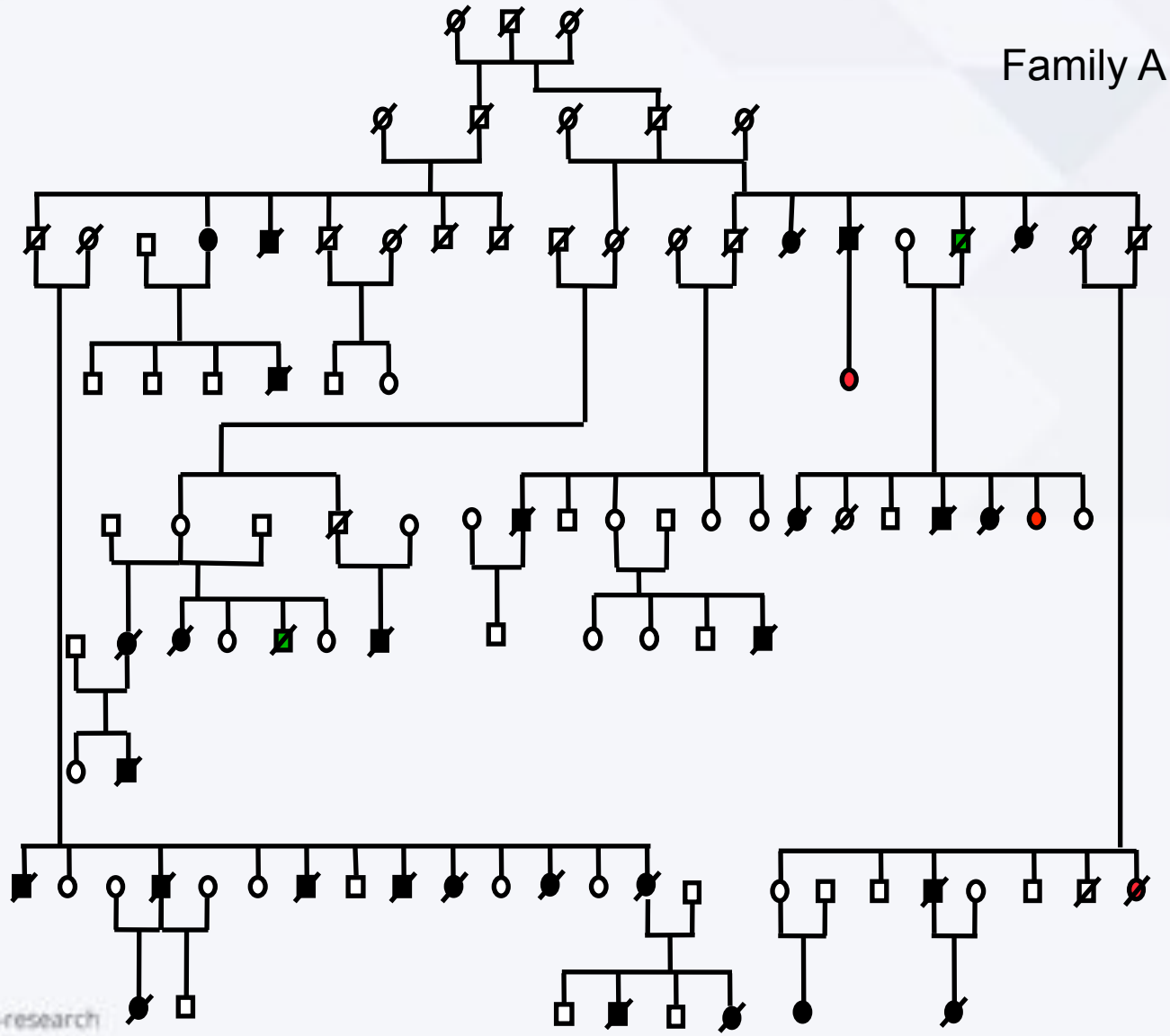
Otago Spotlight Series
Cancer Research

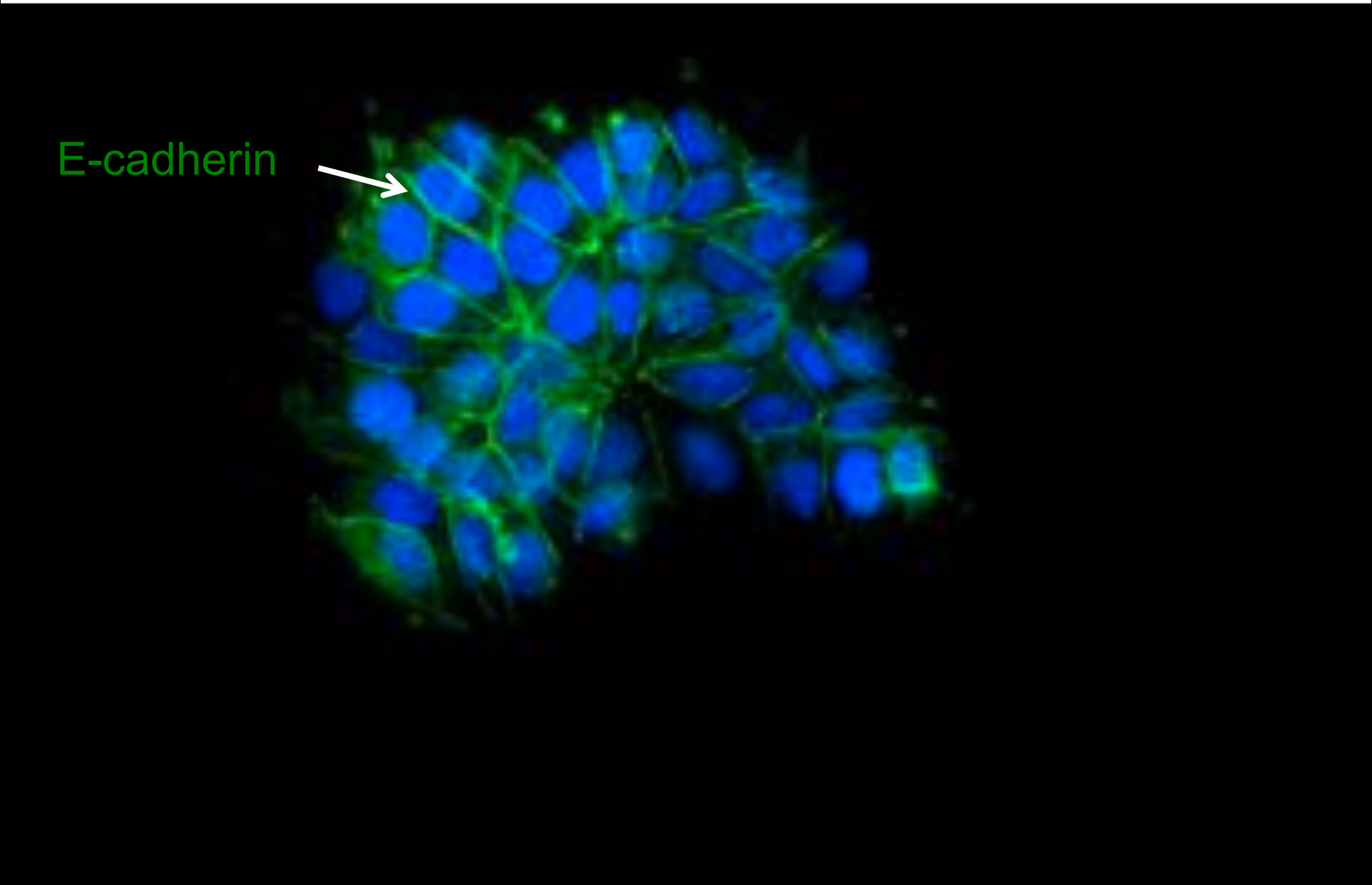
Finding Cancer's Vulnerabilities

Parry Guilford
Cancer Genetics Laboratory

Hereditary diffuse gastric cancer (HDGC)

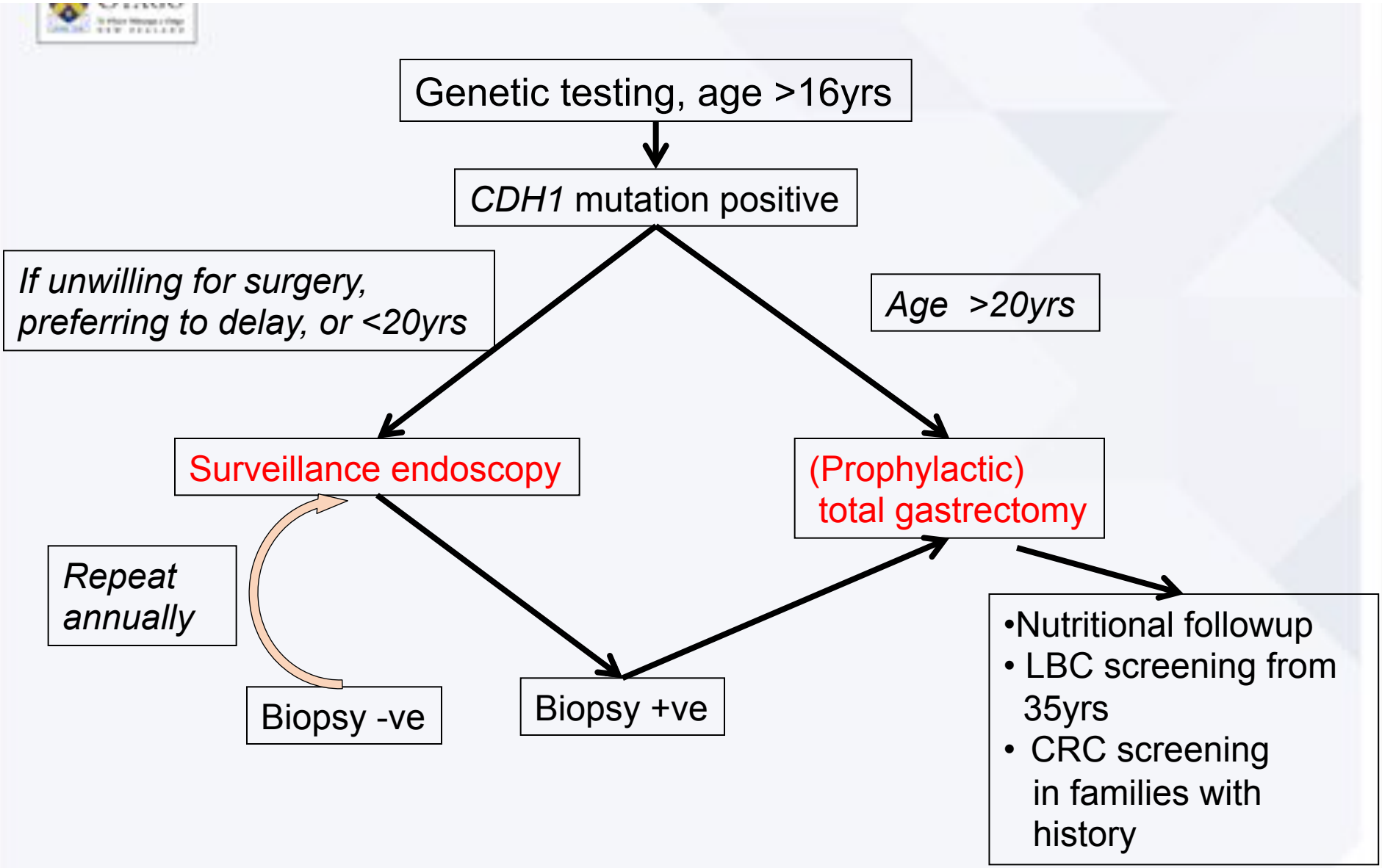


HDGC is caused by inherited mutations in the E-cadherin gene (*CDH1*)

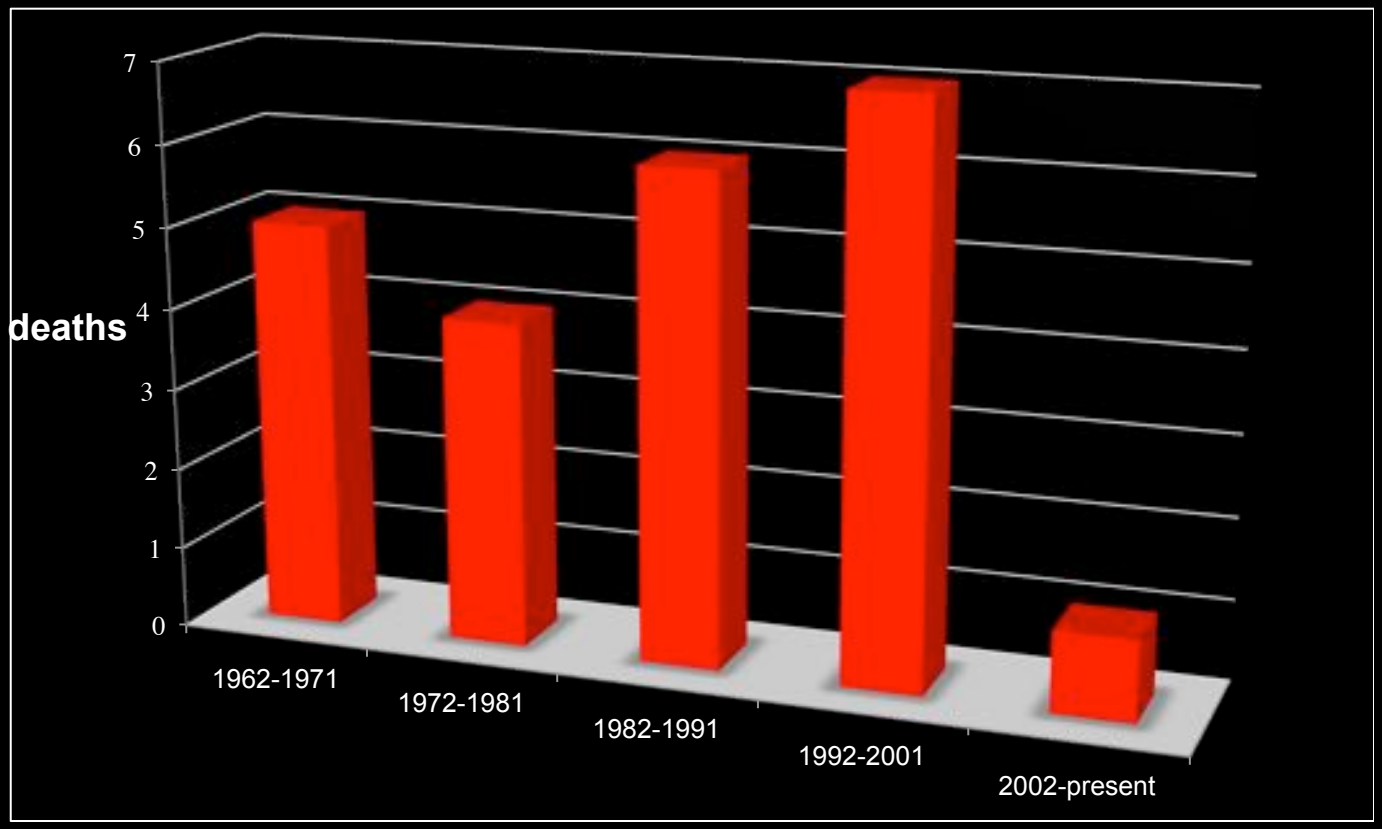


>350 families worldwide

HDGC Clinical Management Guidelines



Family A deaths from stomach cancer

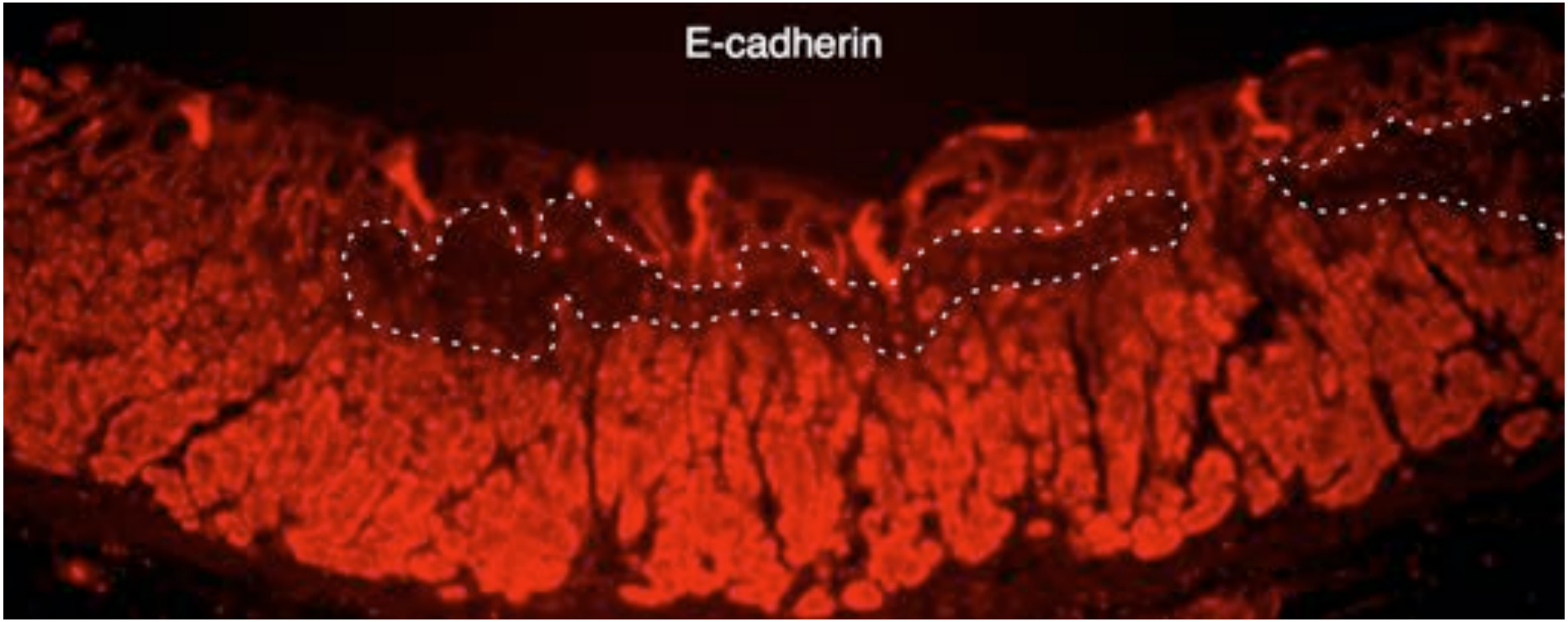


Drug development needs for *CDH1* mutant cancers

- An alternative to total gastrectomy for inherited stomach cancer families

- Treatment for sporadic cancers with *CDH1* mutations
  - -400,000 cases of stomach cancer/yr
  - -150,000 cases of lobular breast cancer/yr

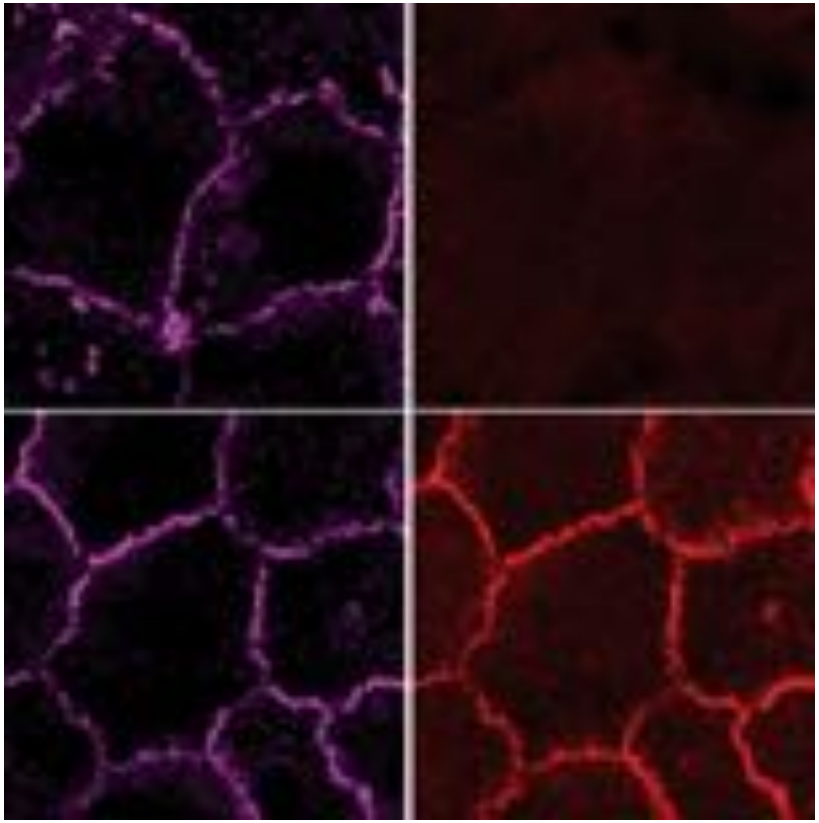
Finding the vulnerabilities



CDH1 mutations reduce the E-cadherin levels in the cell

Whats the target?

Identical human cell lines plus/minus E-cadherin



-

+

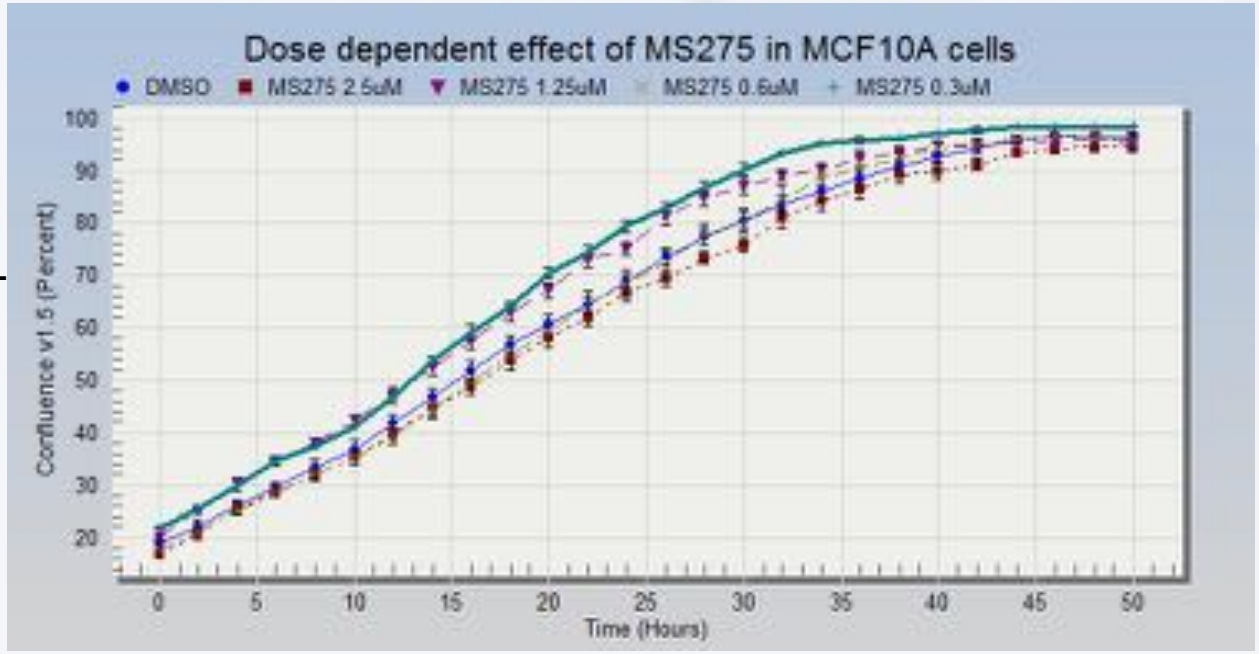
Genetic screen
(18,000 genes)

Known drug screen
(5,000)

Compound screen
(114,000)

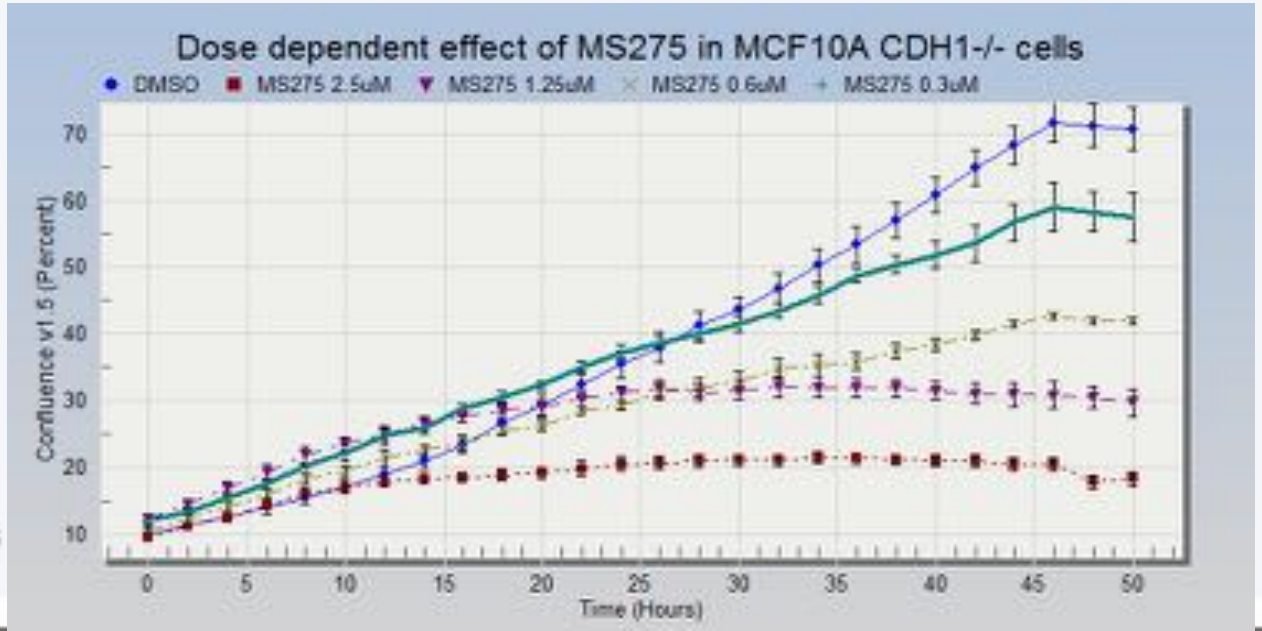
Entinostat (MS275)

E-cadherin +



0.3-2.5uM

E-cadherin -

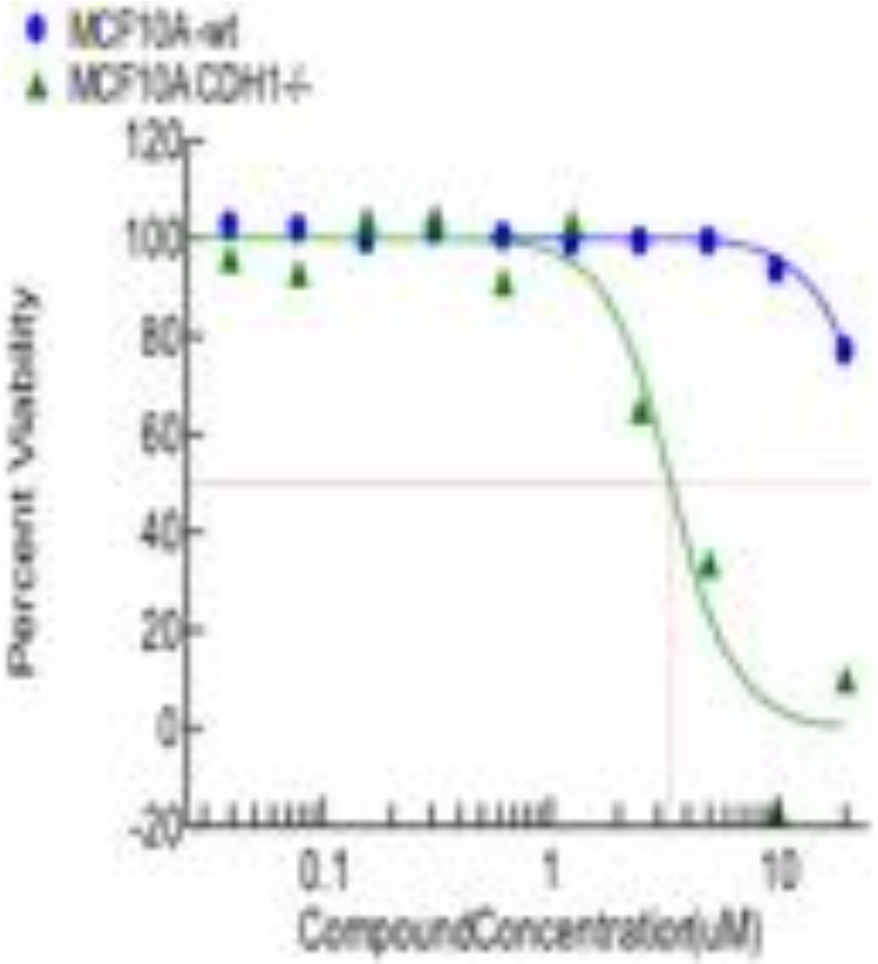


Andrew Single

Novel compounds:

- 114,000 drug-like compounds
- 84 compounds show increased kill on *CDH1-/-* cells

(a)



Henry Beetham

Loss of E-cadherin creates multiple vulnerabilities that can be exploited with drugs

- *Inherited gastric cancer prevention*
- *Treatment of advanced gastric and lobular breast*