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Teams: Leveraging the Power of Collaboration to Advance Your Science

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Division of
GASTROENTEROLOGY
& HEPATOLOGY

Disclosures

- **Gilead Sciences - Grant**
- **Wako Diagnostics - Grant**
- **Inova Diagnostics - Grant**
- **Ariad Pharmaceuticals - Grant**

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Plan

- **Principles to Ponder**
- **My Personal Story**
- **Team Science Stories**

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Key Quotes

“If you want to go fast, go alone; if you want to go far, go together; if you want to go far fast, change the system together.”

“Two are better than one, because they have a good return for their labor. Pity the man who falls and has no one to help him up. A cord of three strands is not easily broken.”

“Getting together is a beginning, staying together is progress, working together is success.” Henry Ford

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What it Takes: Success in Teams

1. **Don’t isolate yourself OR Everyone needs mentors**
2. **Don’t be afraid to share OR Don’t think of yourself only**
3. **Don’t think of your tribe only OR Identity has dark and bright sides**
4. **Don’t slack off OR Put your ham in the game; this is where inspiration comes from**
5. **Don’t overdo work – The counterpoint to “Don’t slack off”; one key is control**

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What it Takes: Success in Teams

6 **Don’t be timid OR Don’t pick a small problem**

7 **Don’t try to do it all by yourself OR Harness the wisdom of diverse teams**

8 **Don’t take all the credit to yourself OR Pay attention to the author list**

9 **Don’t believe everything people tell you**

10 **Don’t give up simply because people don’t believe you or believe in you**

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Outline

- My Story – The village that raised this child
- Hepatitis B Virus Integrations in Liver Cancer
- Fluorescence In Situ Hybridization for Diagnosis of Pancreatobiliary Cancer
- The Global HCC BRIDGE Study
- The Cancer Genome Atlas Projects for Liver and Biliary Cancer
- Global – This is no time for small dreams

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Ghana

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The Old Man & His Son

Rev. J. T. Roberts
1870-1964

Dr. Lewis R. Roberts
1918-2010

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A Curious Child

Adeline Roberts

Early Years – What my mother taught me

- Education counts
  - learn vicariously
- Family counts
- Take individual responsibility

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Who Came the Farthest?

- Kumasi, the Ashanti capital
  - Read epilogue of “In my father’s house” by Anthony Appiah

- Prempeh College
  - Suban ni Nimdee
  - Character and Leadership

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University of Ghana Medical School

"You should consider a career in medical research."

Stephen Addae

"You must be seen to be keen."

Kenneth Adjepong-Yamoah

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"You must be seen to be keen."

Kenneth Adjepong-Yamoah

A young man with liver cancer.

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Iowa? Are you going to study corn?

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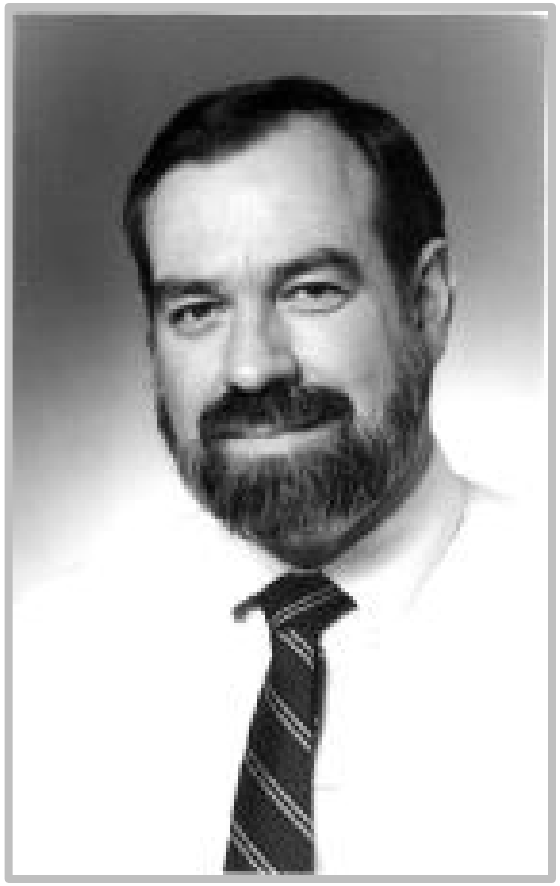
Graduate School

“Lewis, all the easy experiments have been done already.”

Rich Maurer



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Transition to Clinical Training

"Where would you go if you could go to the best possible place?"

"Let them say no."

Lene Holland

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Residency

"This would be taking a risk, but let's do it."

Anonymous interviewer

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Clinician-Investigator Fellowship

"It seems to me you just need to keep pressing on."

Nick LaRusso

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Junior Faculty "Got mentors?"

Chuck Rohren

Greg Gores

Juanita Merchant

Patrick Kamath

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Embrace New Ideas

“Dr. DeBakey was never afraid to challenge the status quo, often going against the tide ... Some times his colleagues did not really accept his visionary ideas, particularly as he propelled beyond the boundaries of existing scientific dogma.”

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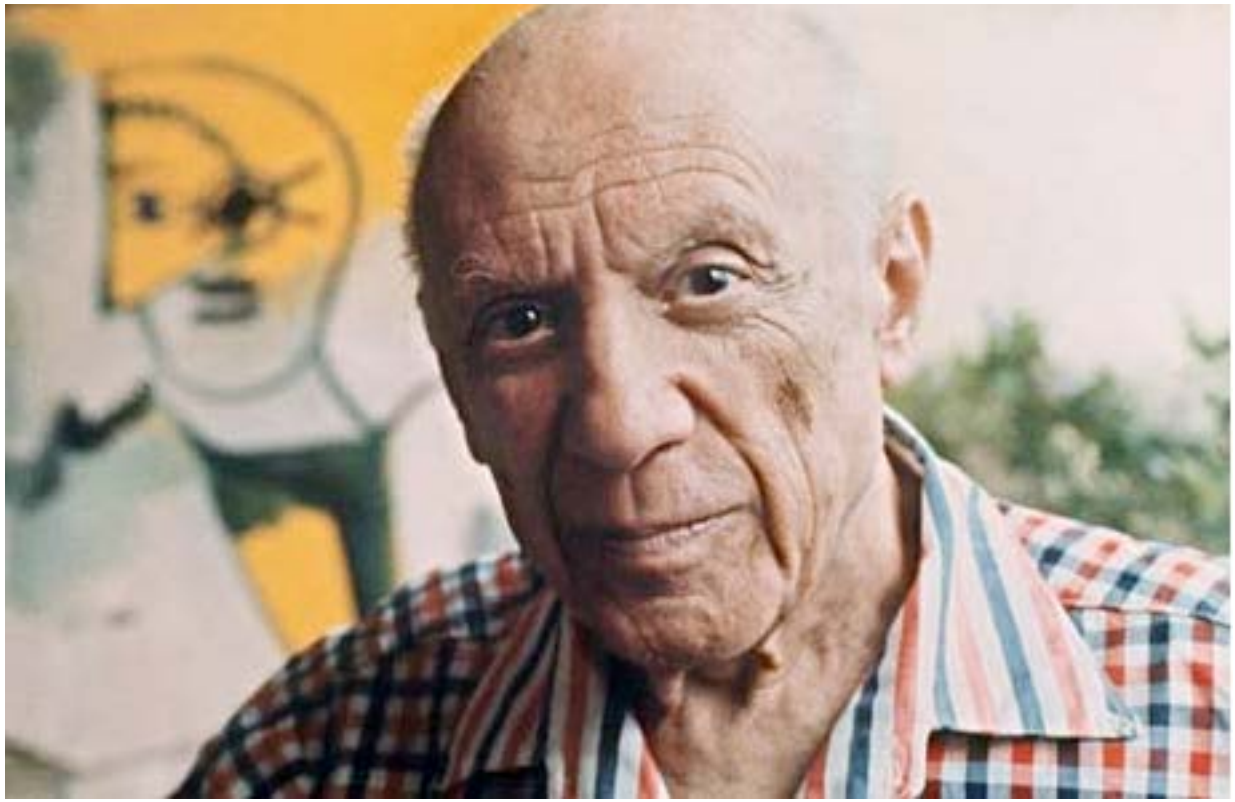
Keep an Eye Out for Inspiration



“Inspiration comes to me often; and when it comes, it usually finds me working.”

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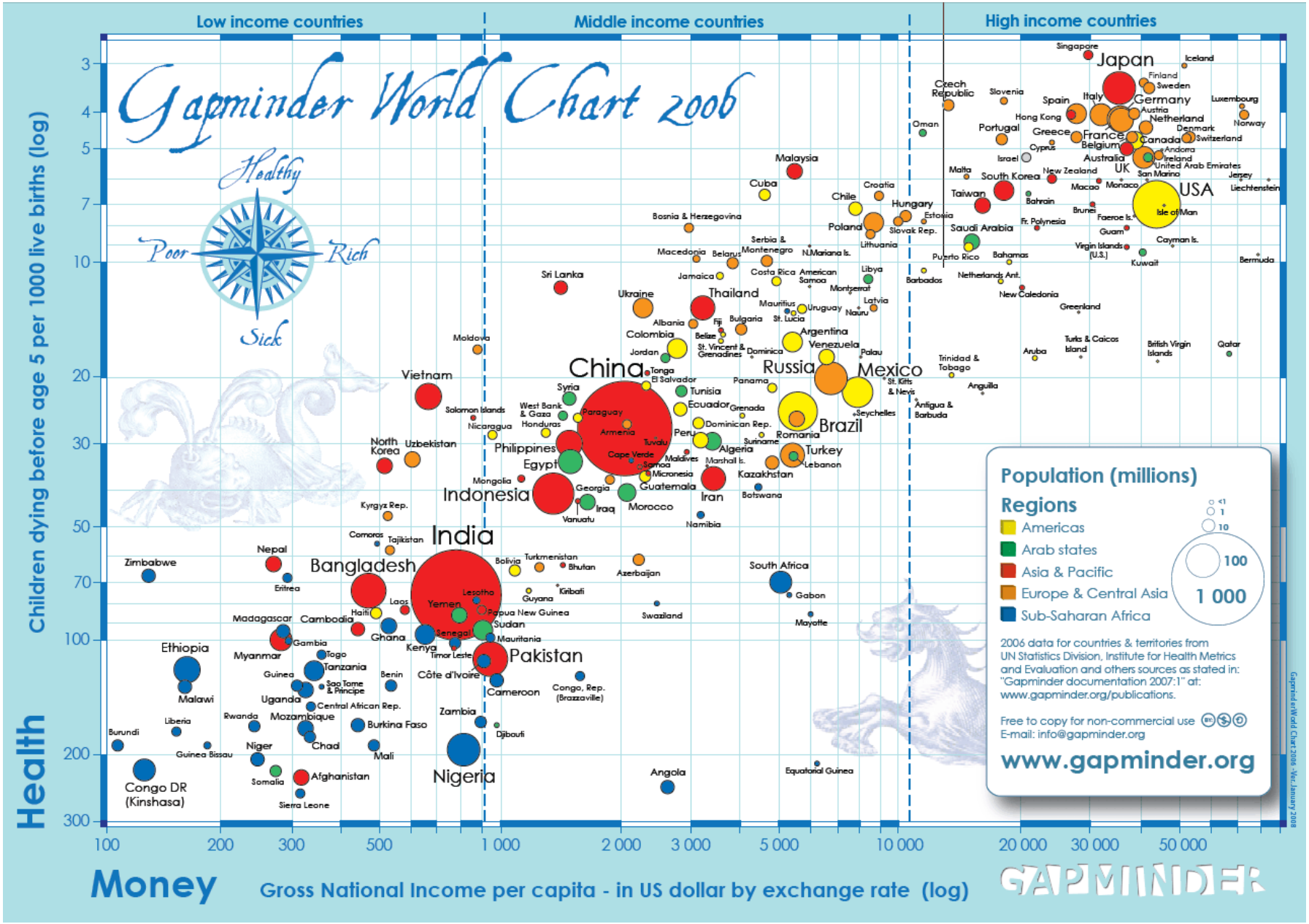
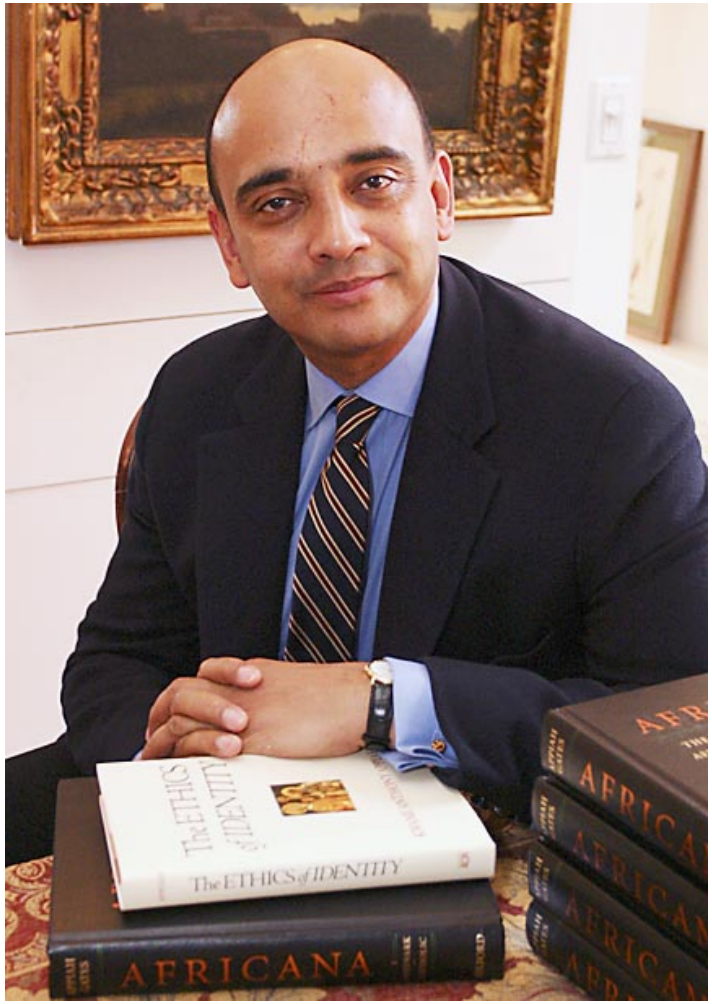
Global Disparities in Wealth and Health



Aspire to the Ethical Life



Anthony Appiah

"There are certain basic resources to which every human being is entitled, in virtue, in part, of their dignity as persons. They are the resources that each person needs to make a dignified life, to pursue the individuality to which we are all entitled. We owe it to each other to make sure that everyone on the planet has these basic resources, and we are clearly far from having achieved that. Until we do, there is, I think, a moral stain on the achievements of each of us who has been granted those resources and more. Part of the reason we do so much less about this than we should, I think, is the power of national and more local identities to blind us to the significance of the suffering of strangers. So identity has a dark side.."

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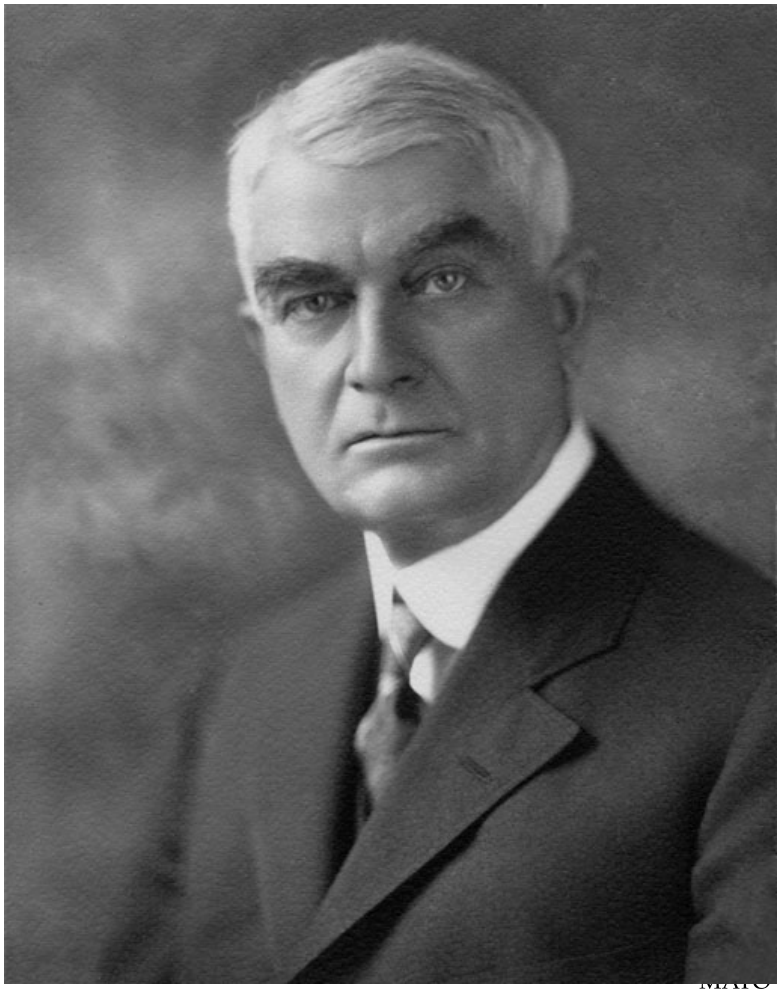
The Bright Side of Identity
Obligation to Prevent Needless Death

"Our father recognized certain definite social obligations. He believed that any man who had better opportunity than others, greater strength of mind, body, or character, owed something to those who had not been so provided; that is, that the important thing in life is not to accomplish for one's self alone, but for each to carry his share of collective responsibility"

"We know how hard it is for those who have have the misfortune of deaths in their families, of deaths that might have been avoided. What better could we do than take young men and help them to become proficient in the profession so as to prevent needless deaths?"



William J. Mayo, 1917, 1934

“How relevant am I to those with the least resources?”

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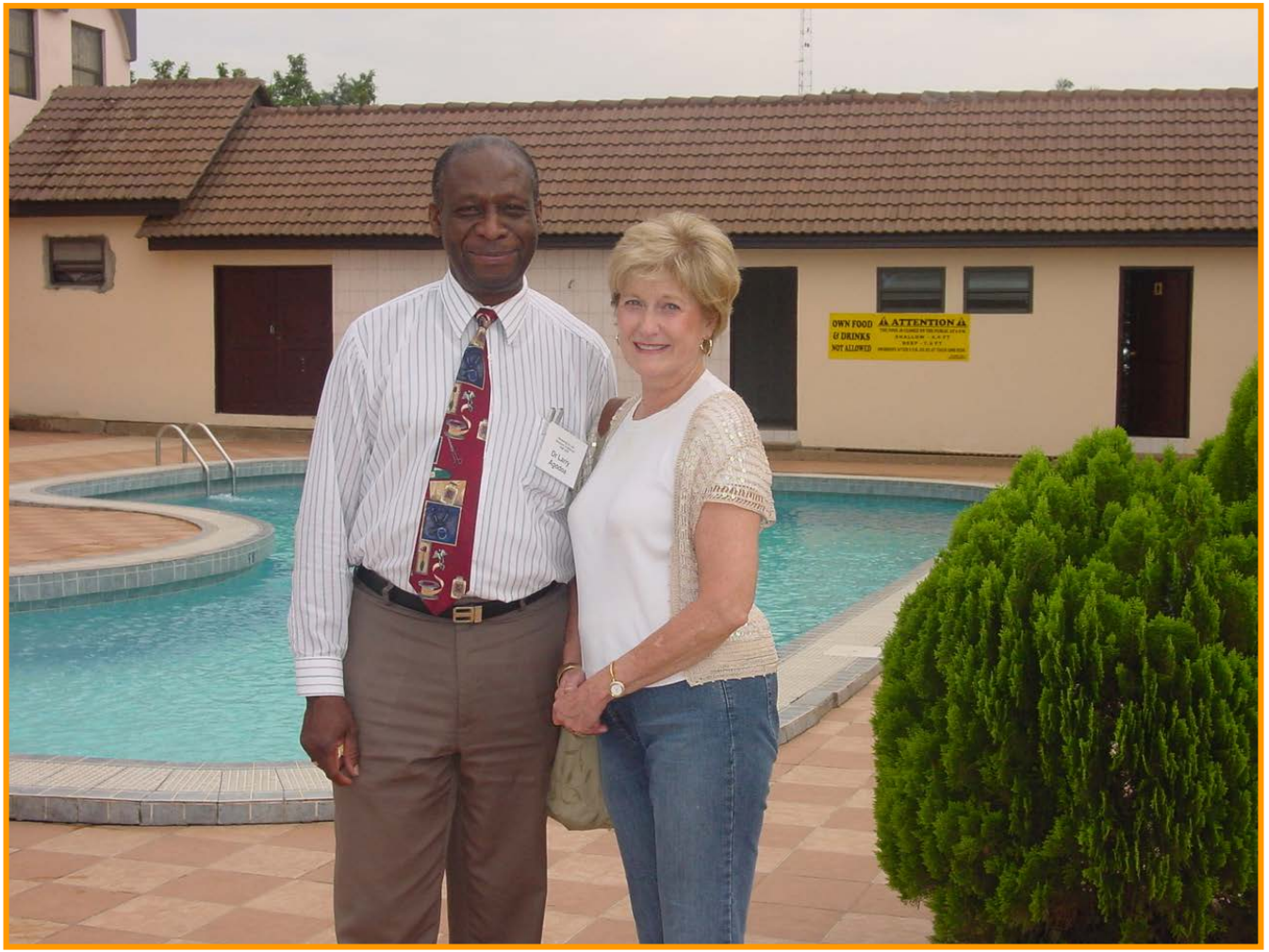
Africa Partners Medical
Make the Brain Drain a Circulation

“I struggled with this when thinking of my own career years ago as to whether my talents would be best used back in my native Mississippi or on the other hand should I go where the best intellectual pursuits and opportunities are.” Eddie Greene, MD

Some People Just Can’t Help Helping



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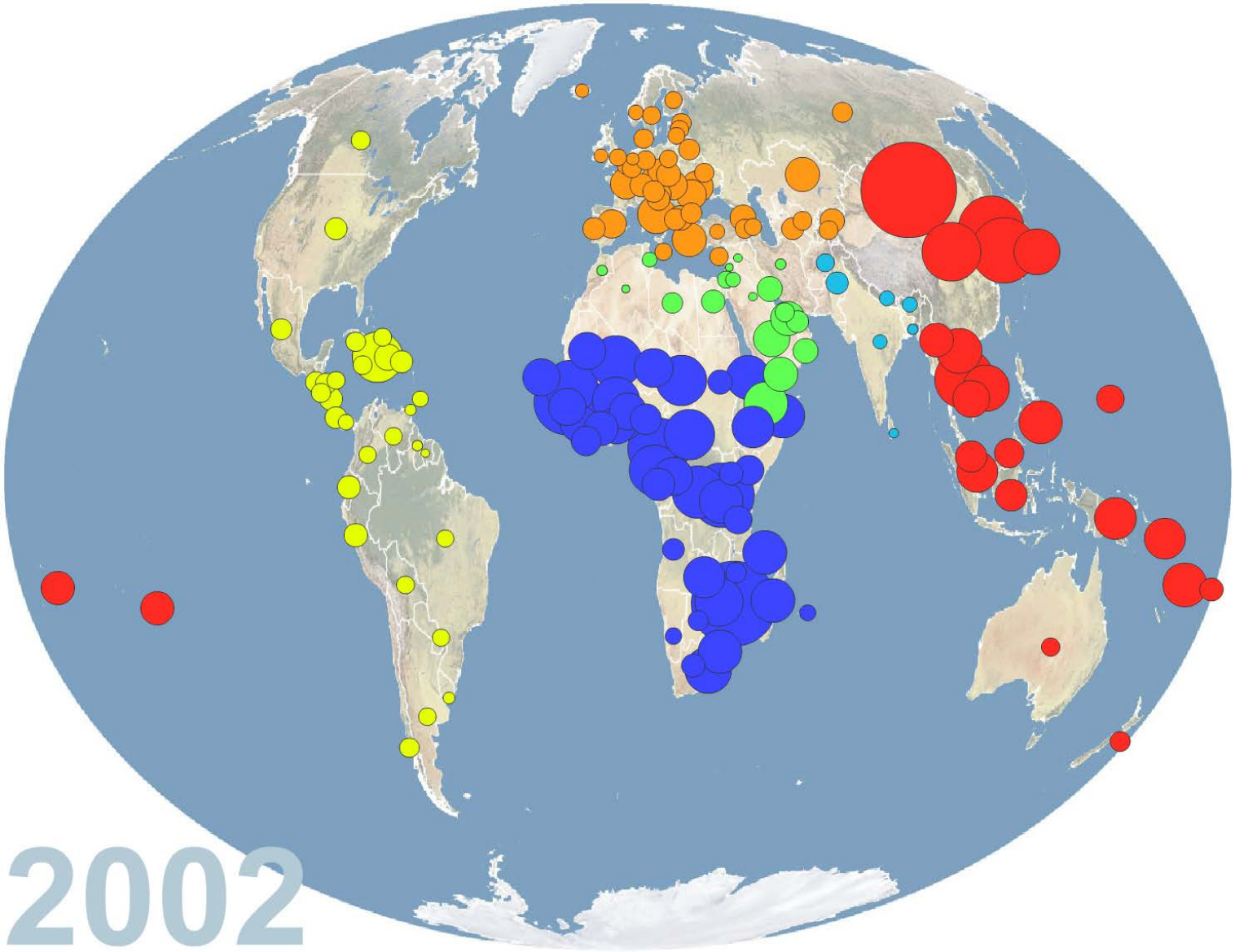
Why Liver Cancer? The Global Epidemiology of Hepatocellular Carcinoma

- 6th most common cancer worldwide
- 2nd most common cause of death from cancer
- Over 800,000 new cases worldwide in 2012
- US incidence has tripled in the past 30 years, due to the cohort of chronic hepatitis C patients infected between 1960 and 1990
- Metabolic syndrome, diabetes & NASH are important new risk factors

Global Incidence Rates of HCC in Men



www.gapminder.org

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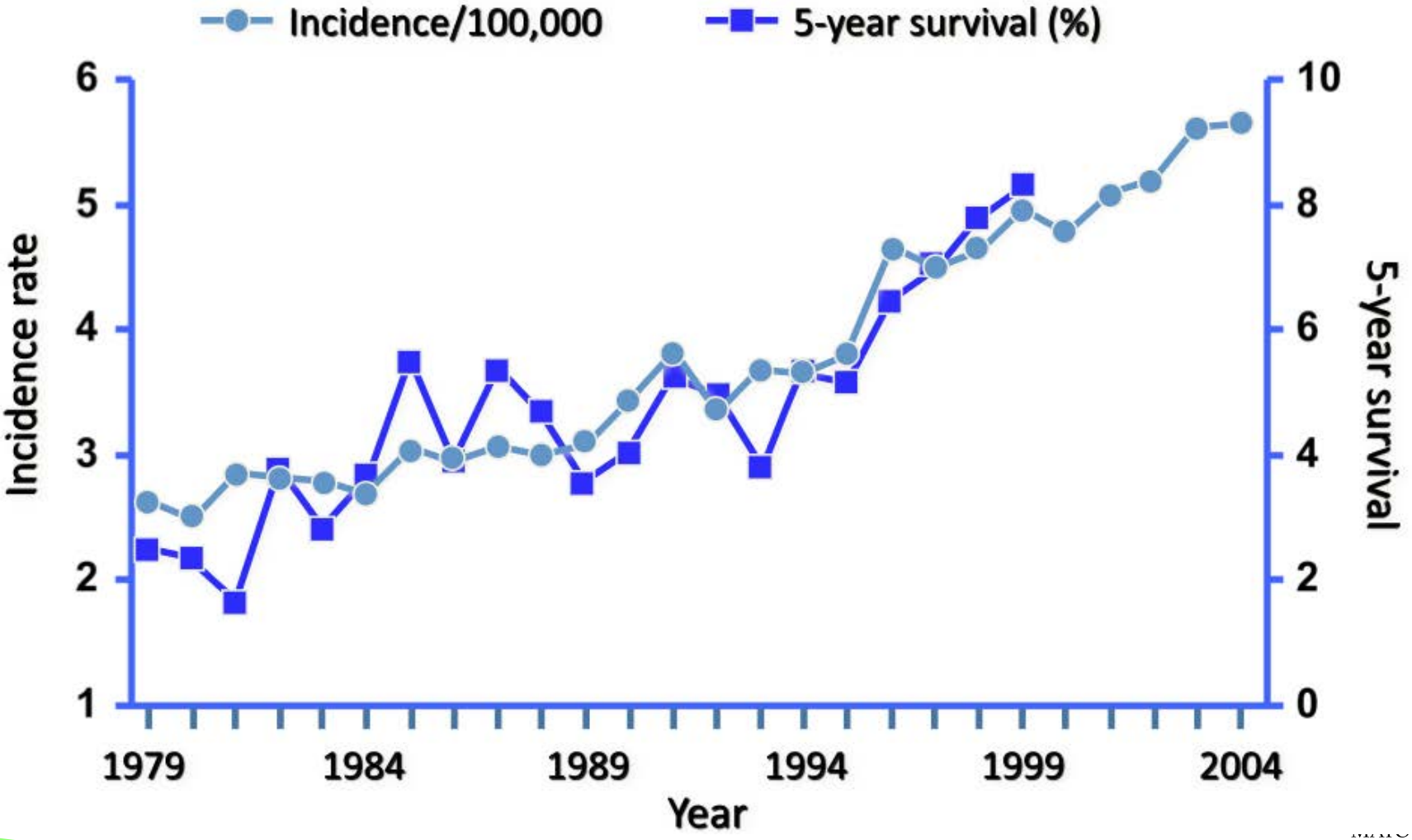
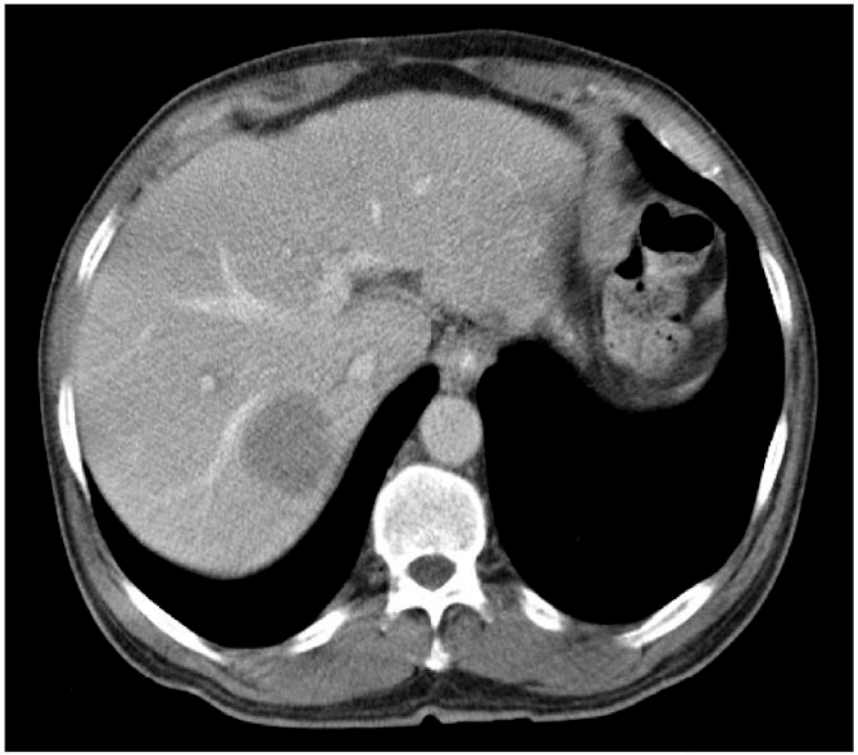
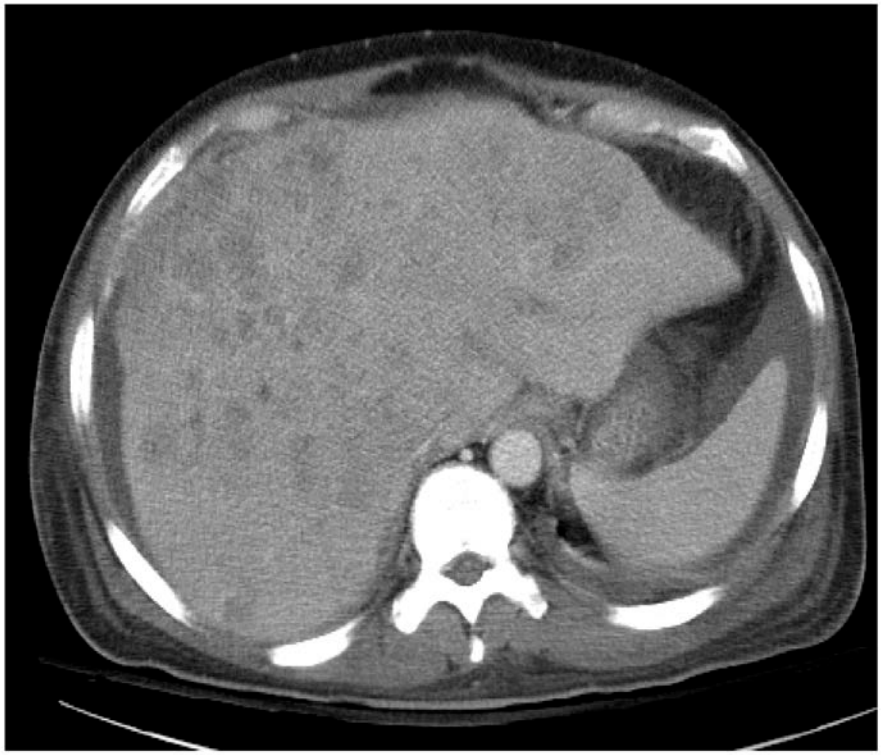
HCC Incidence has Tripled in the US Survival is Improving but Still Very Poor



Everhart and Ruhl: Gastroenterol 136:1134, 2009

Key Challenges: Prevention, Early Diagnosis and Treatment of Advanced HCC





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Program Goals

- Identify and characterize novel genes involved in the pathogenesis of hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC)
- Use new information to support translational efforts at prevention, early diagnosis, prognostic prediction, and clinical management of HCC and CC
- Strong focus on facilitating national and international collaborations

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Approach

- Use a variety of techniques for gene identification in HCC
- Develop cancer genetics, cell and molecular biology, and bioinformatics capabilities for characterizing gene alterations and roles in HCC pathogenesis
- Develop patient resources to support basic and clinical research

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Clinical Research Resources

- International Hepatobiliary Cancers Registry
  - Demographic information, past history, family history, risk factors and exposures
  - Episode of care: symptoms, signs, lab results, radiology, diagnoses, therapy, quality of life
- Biorepository
  - Blood for DNA, plasma and serum
  - Tumor and adjacent benign tissue from surgical resections and liver transplantation
  - Patient derived xenografts and cell lines
  - Bile, urine, stool
  - Participating in TCGA HCC and CCA projects
- Epidemiology, Statistics, and Outcomes
- Clinical Trials Capability of NCCTG/Alliance

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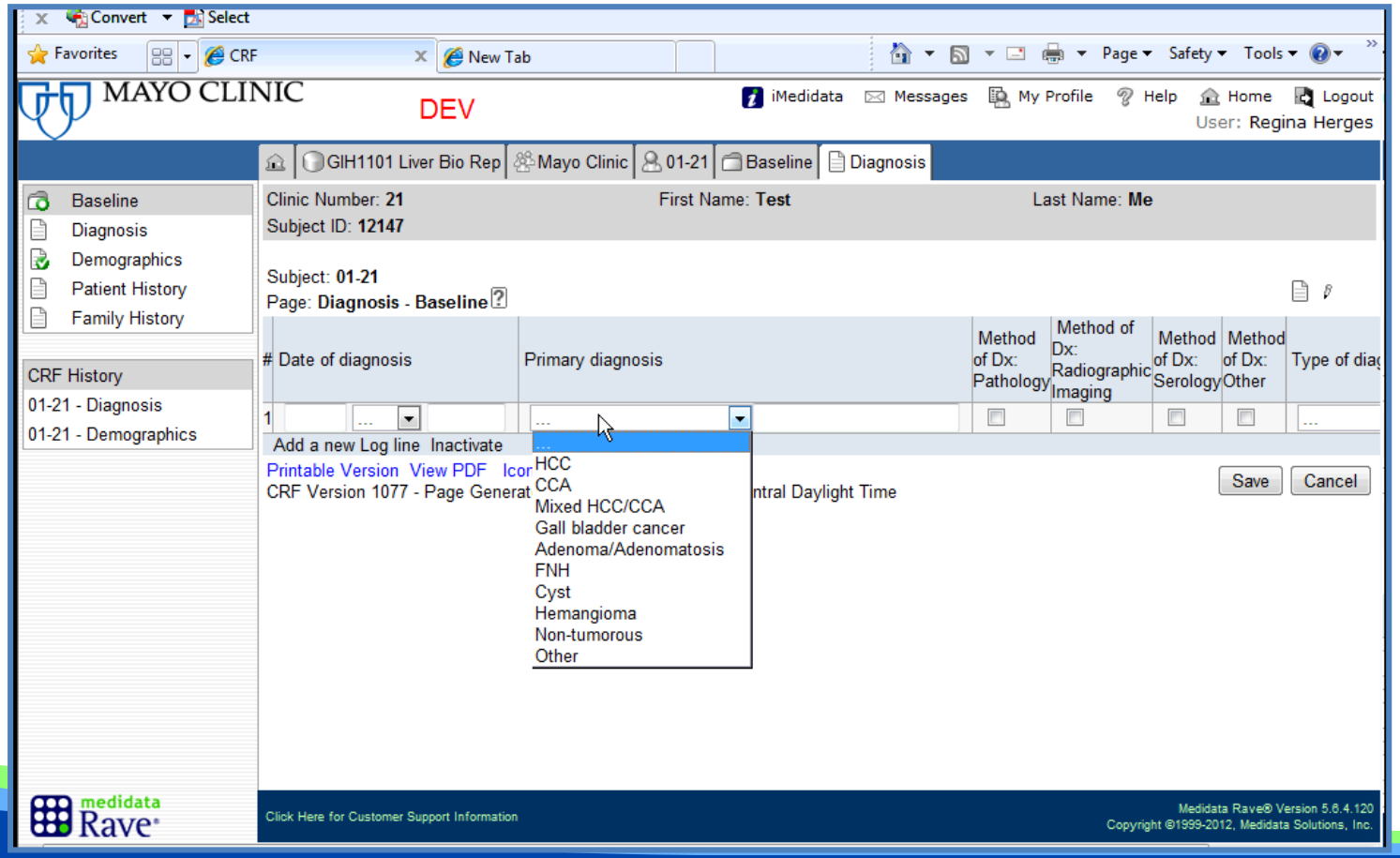
Online Hepatobiliary Cancers Registry with Electronic Data Capture

- Centralized registry to promote national and international collaboration
- Complies with HIPAA Privacy & Security requirements.



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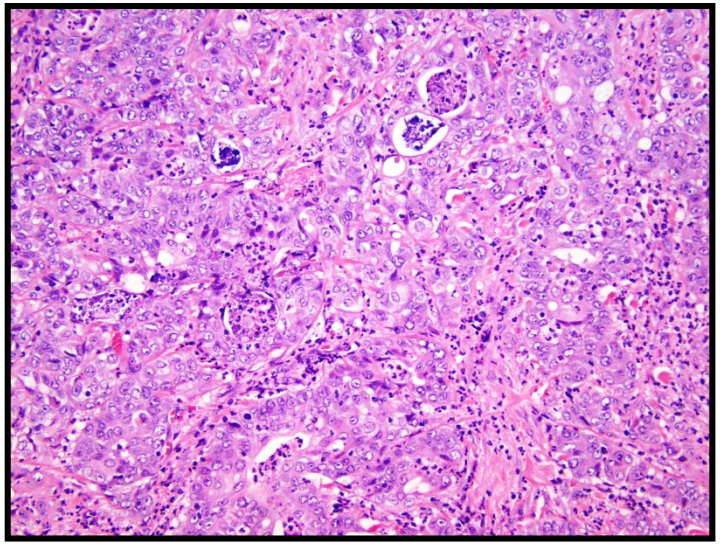
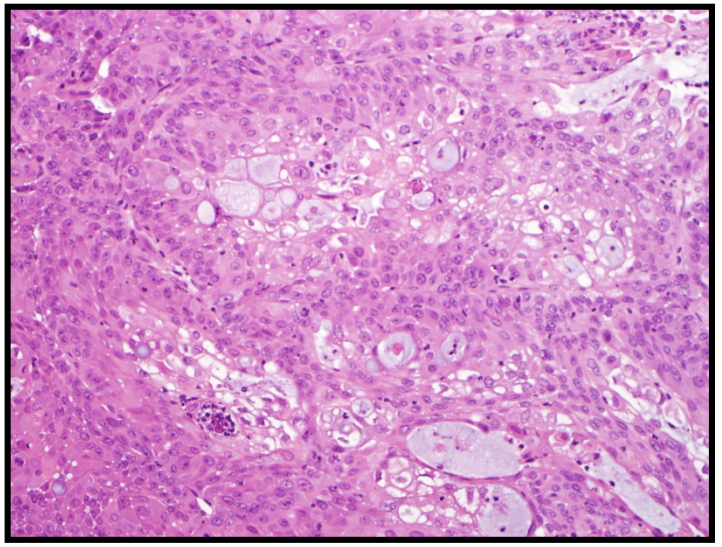
Patient Derived Xenografts

Original Human Tumor

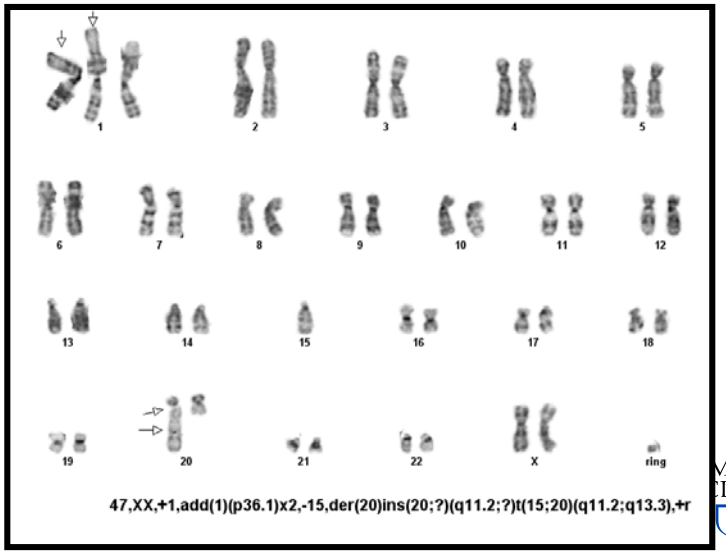


PDX



Tumor SQ in Nude Mouse

Karyotype



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Strong Emphasis on Collaborations

nature medicine

A novel prognostic subtype of human hepatocellular carcinoma derived from hepatic progenitor cells

Ju-Seog Lee[1], Jeonghoon Heo[1], Louis Libbrecht[2], In-Sun Chu[3], Pal Kaposi-Novak[1], Diego F Calvisi[1], Arsen Mikaelyan[1], Lewis R Roberts[4], Anthony J Demetris[5], Zongtang Sun[6], Frederik Nevens[2], Tania Roskams[2] & Snorri S Thorgeirsson[1]

GASTROENTEROLOGY 2012;142:1021–1031

Genomic and Genetic Characterization of Cholangiocarcinoma Identifies Therapeutic Targets for Tyrosine Kinase Inhibitors

JESPER B. ANDERSEN,* BART SPEE,‡ BORIS R. BLECHACZ,§ ITZHAK AVITAL,‖ MINA KOMUTA,‡ ANDREW BARBOUR,¶ ELIZABETH A. CONNER,* MATTHEW C. GILLEN,* TANIA ROSKAMS,‡ LEWIS R. ROBERTS,§ VALENTINA M. FACTOR,* and SNORRI S. THORGEIRSSON*

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Strong Emphasis on Collaborations

nature genetics

Exome sequencing identifies frequent inactivating mutations in *BAP1*, *ARID1A* and *PBRM1* in intrahepatic cholangiocarcinomas

Yuchen Jiao[1–3,20], Timothy M Pawlik[3,4,20], Robert A Anders[3,5,20], Florin M Selaru[6], Mirte M Streppel[5], Donald J Lucas[7], Noushin Niknafs[8], Violeta Beleva Guthrie[8], Anirban Maitra[3,5], Pedram Argani[3,5], G Johan A Offerhaus[9], Juan Carlos Roa[10], Lewis R Roberts[11], Gregory J Gores[11], Irinel Popescu[12], Sorin T Alexandrescu[12], Simona Dima[12], Matteo Fassan[13,14], Michele Simbolo[13,14], Andrea Mafficini[13], Paola Capelli[14], Rita T Lawlor[13,14], Andrea Ruzzenente[15], Alfredo Guglielmi[15], Giampaolo Tortora[16], Filippo de Braud[17], Aldo Scarpa[13,14], William Jarnagin[18], David Klimstra[19], Rachel Karchin[8], Victor E Velculescu[1–3], Ralph H Hruban[3,5], Bert Vogelstein[1–3], Kenneth W Kinzler[1–3], Nickolas Papadopoulos[1–3] & Laura D Wood[5]

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Strategies for Identifying Novel Genes Involved in Liver Carcinogenesis

- Genes located at the sites of hepatitis B viral integration in HBV-induced HCCs, e.g. hTERT (Ferber et al. Oncogene 2003;22:3813-20)
- Genes located within common chromosomal fragile sites, e.g. Parkin (Wang et al. Genes Chromosomes Cancer 2004;40:85-96)
- Genes shown to be frequently up- or down-regulated in HCCs, e.g. AXIN2 (Taniguchi et al. Oncogene 2002;21:4863-71)
- Genes implicated in the pathogenesis of other epithelial cancers, e.g. SULF1 & SULF2 (Lai et al. Gastroenterology 2004;126:231-248; Lai et al. Gastroenterology 2006;130:2130-2144; Lai et al. Hepatology 2008; 47:1211-1222; Lai et al. Hepatology 2010; 52:1680-1689)

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Does HBV Integrate into Random Sites in the Human Genome?

Oncogene (2003) 22, 3813–3820

www.nature.com/onc

Integrations of the hepatitis B virus (HBV) and human papillomavirus (HPV) into the human telomerase reverse transcriptase (hTERT) gene in liver and cervical cancers

MJ Ferber[1,2,10], DP Montoya[3,10], C Yu[3], I Aderca[3], A McGee[1], EC Thorland[1], DM Nagorney[4], BS Gostout[5], LJ Burgart[6], L Boix[7], J Bruix[7], BJ McMahon[8], TH Cheung[9], TKH Chung[9], YF Wong[9], DI Smith[1], and LR Roberts*[,3]

"Our work supports the hypothesis that the sites of oncogenic viral integration are nonrandom and that genes at the sites of viral integration may play important roles in carcinogenesis."

Ferber et al: Oncogene, 2003

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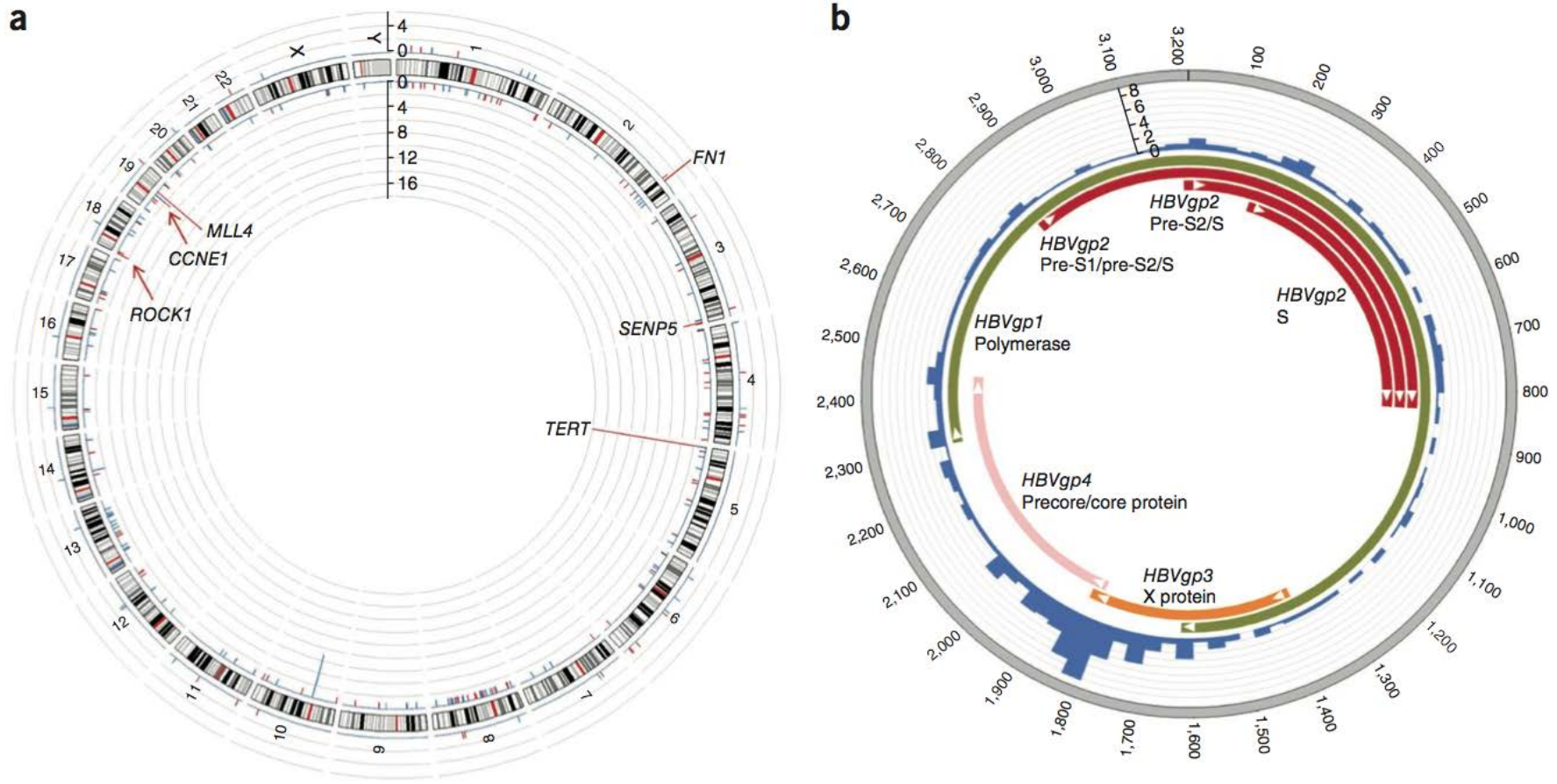
NGS Confirms Recurrent HBV Integrations into the Human Genome in HCC



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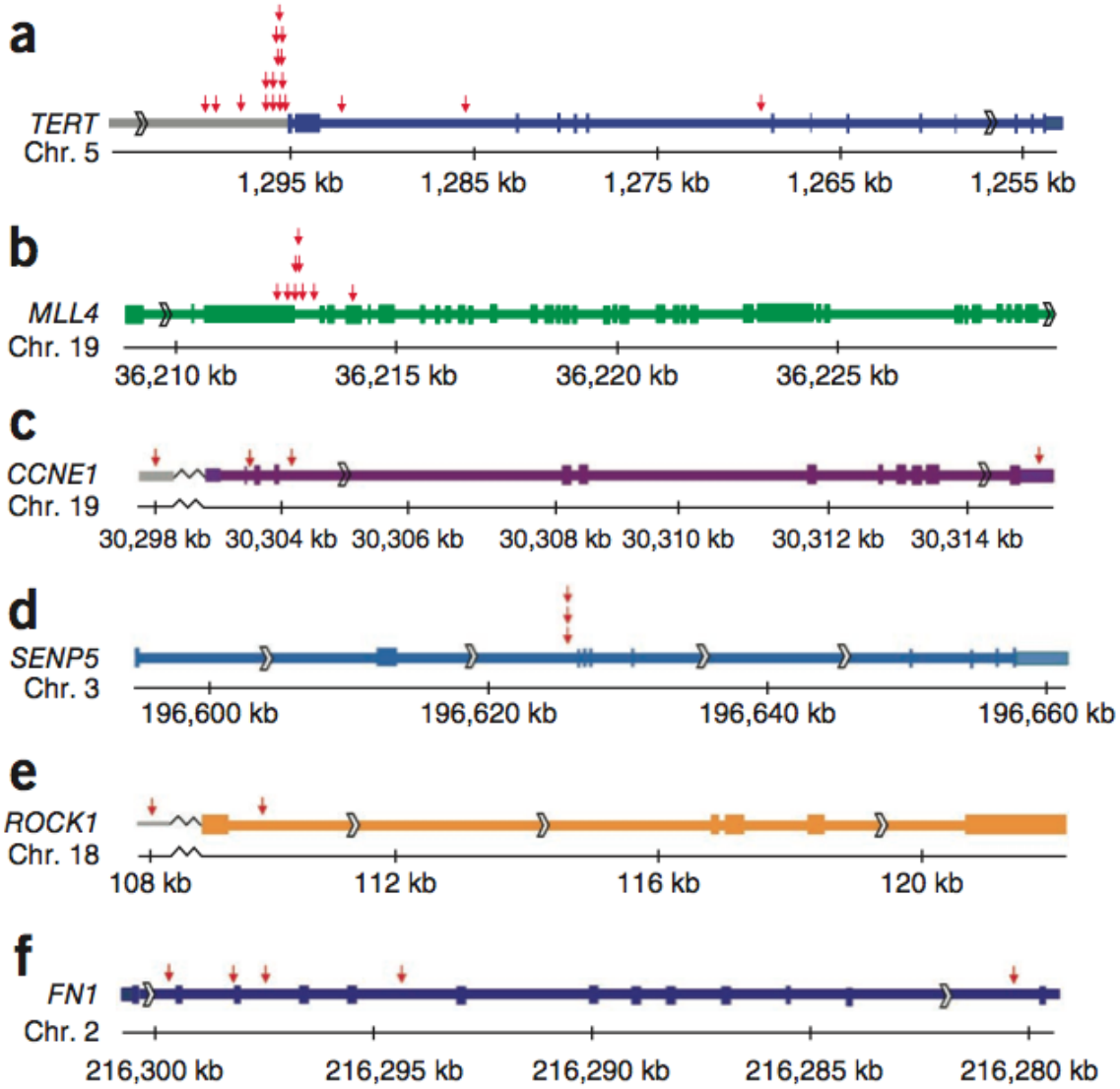
TERT is a Target for HBV Integrations



Ferber et al: Oncogene 2003; Sung et al: Nature Genetics, 2012

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Fluorescence In Situ Hybridization for Diagnosis of Pancreatobiliary Cancer

- Classification of cholangiocarcinoma (CCA)
- Why diagnosis of perihilar CCA is hard
- The Eureka Moment
- Focus on the Feasible First
- Don’t lose sight of the dream: PB FISH

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Classification of Cholangiocarcinoma (CCA)

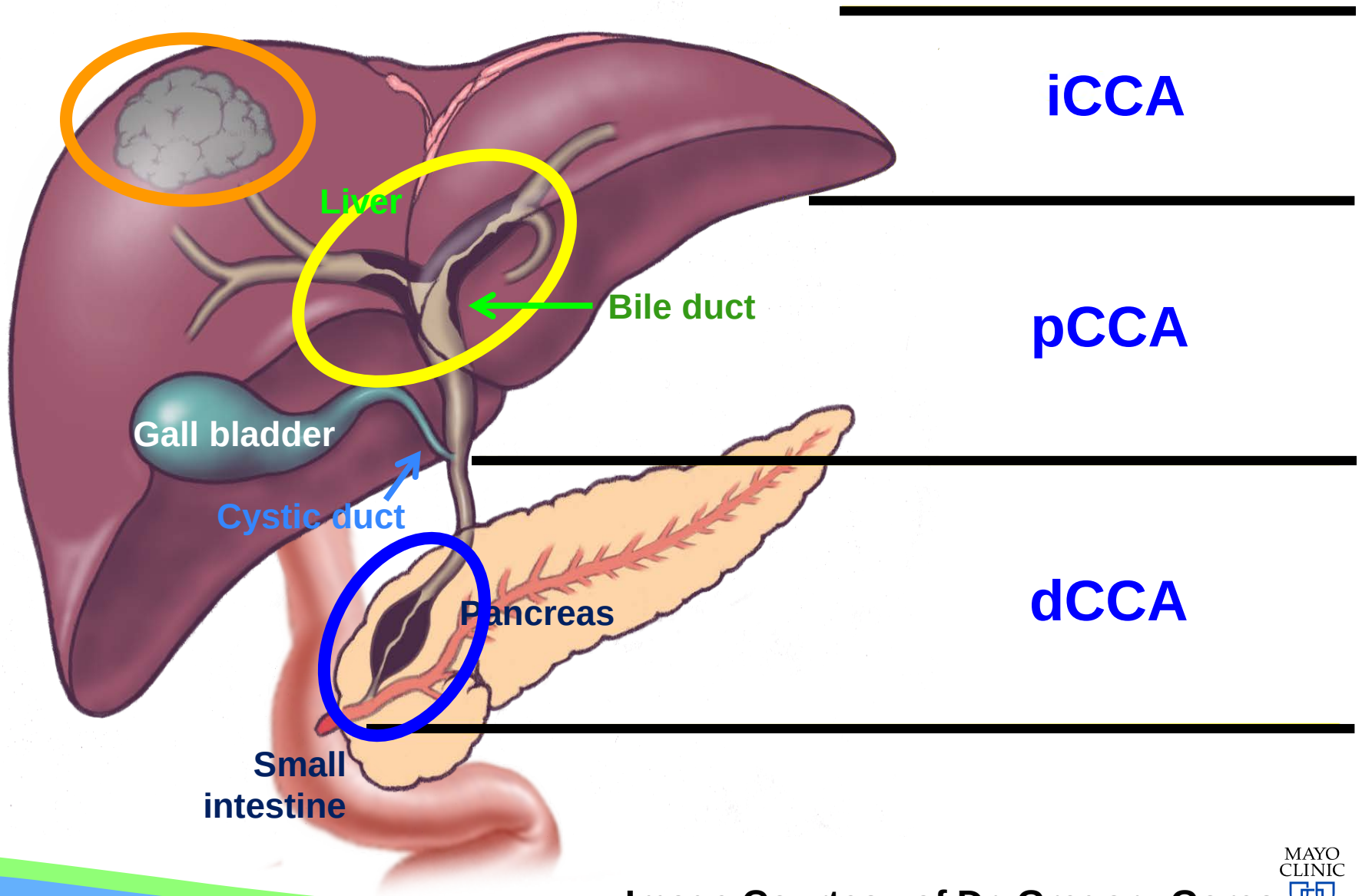

Image Courtesy of Dr. Gregory Gores

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Patients with CCA have Poor Survival Outcome

Green figures represent those who have survived 5 years or more
Gray figures represent who have died from cholangiocarcinoma (CCA)

Median survival is only 8 months

Everhart J, et al. Gastroenterology 2009;136:1134-44.
Modified from: http://seer.cancer.gov/statfacts/html/livibd.html

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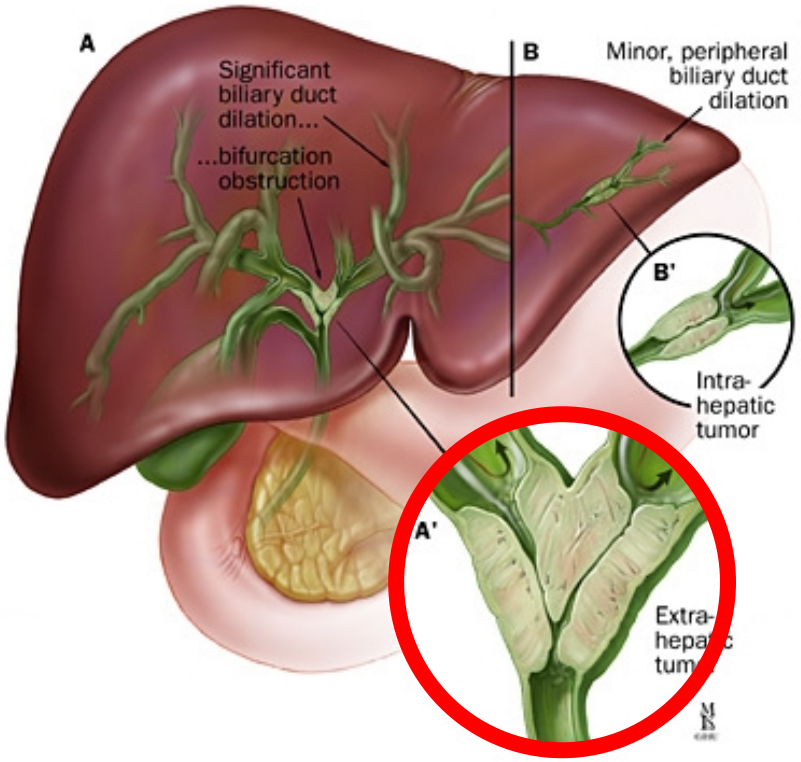
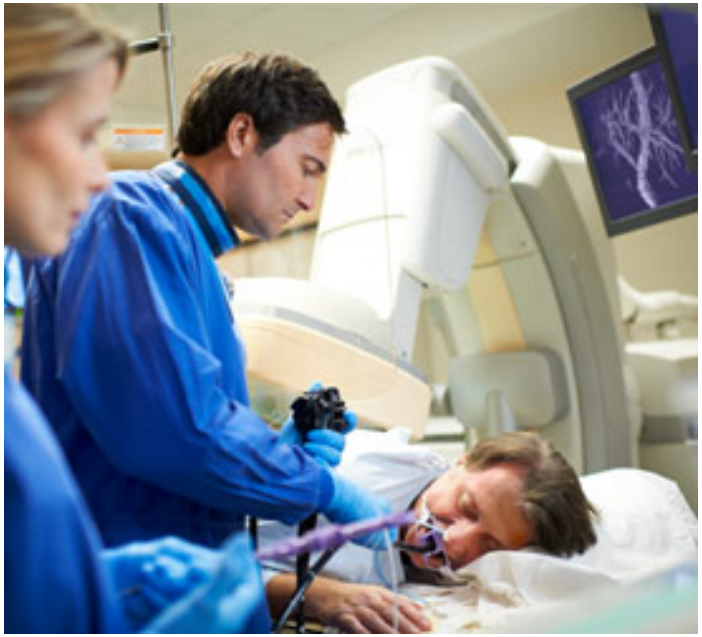
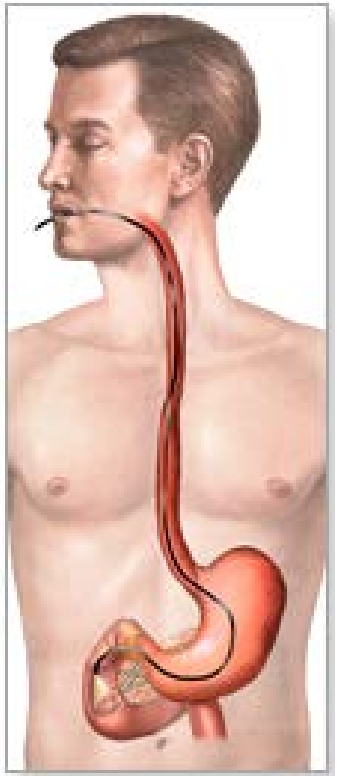
Diagnosis of Malignant Biliary Strictures

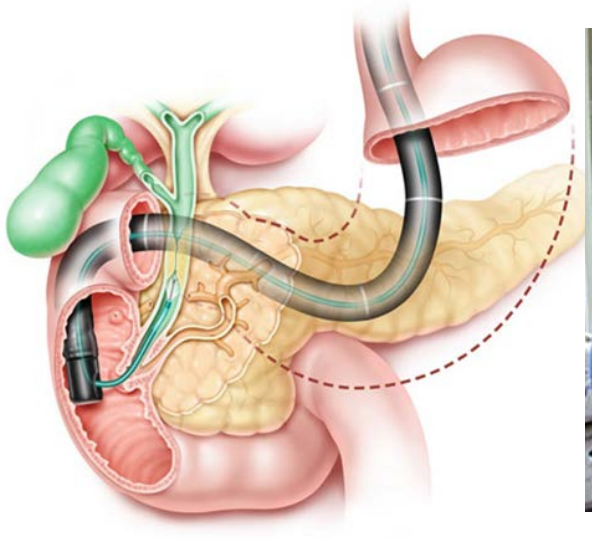


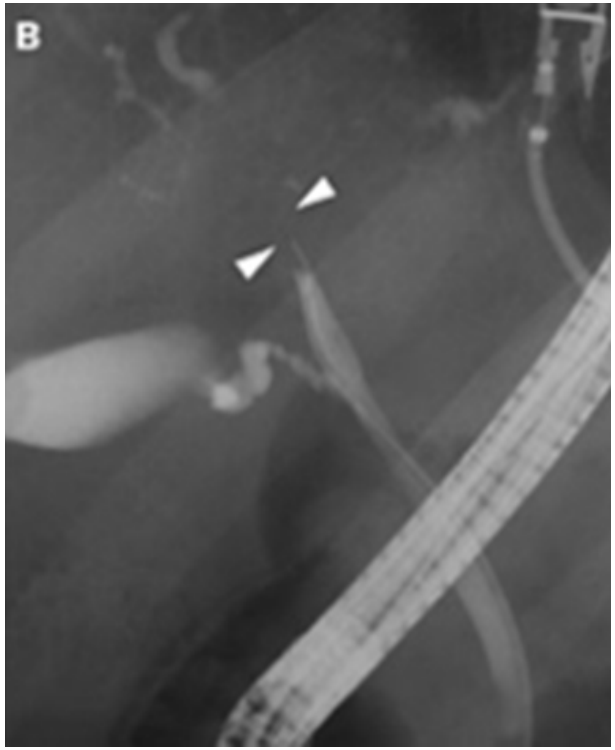


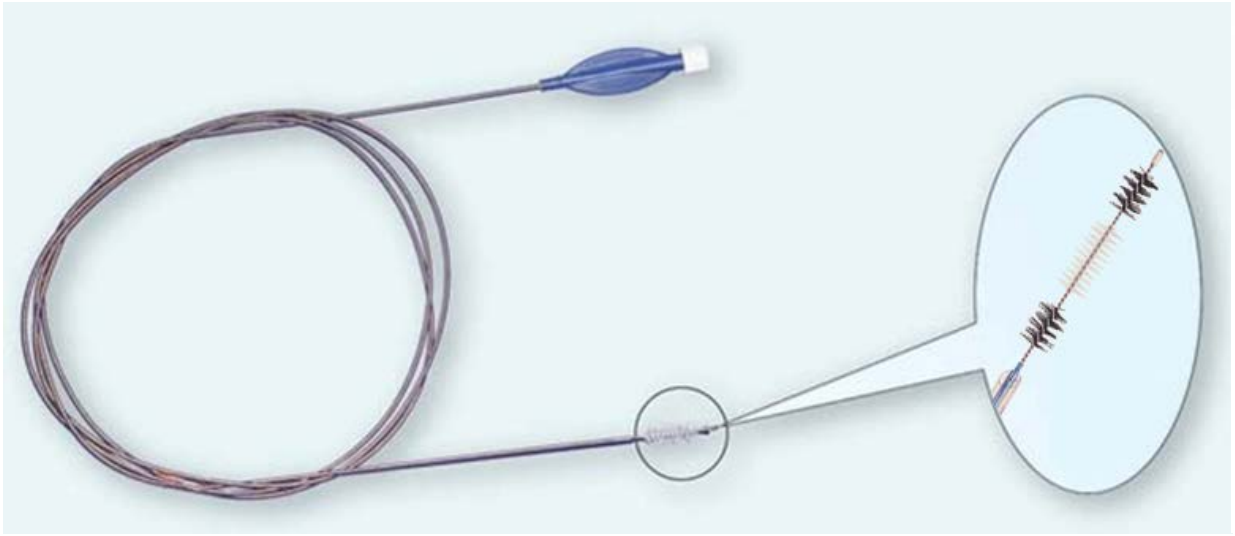


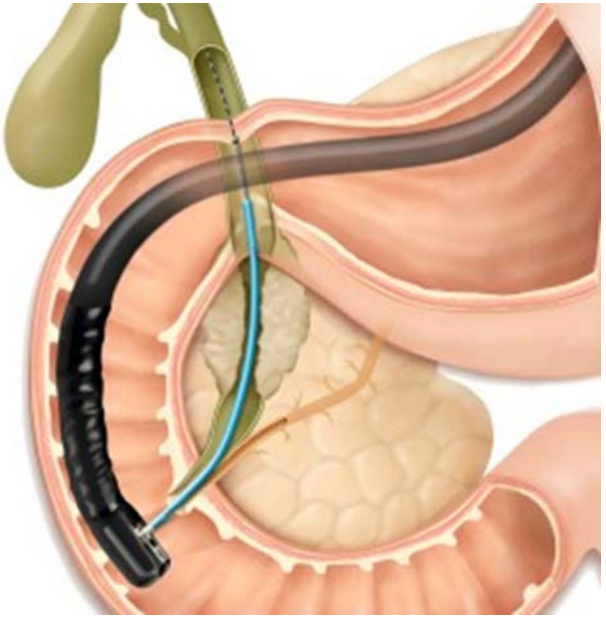
Cell and tissue samples can be obtained during Endoscopic Retrograde Cholangiopancreatography (ERCP)

ERCP



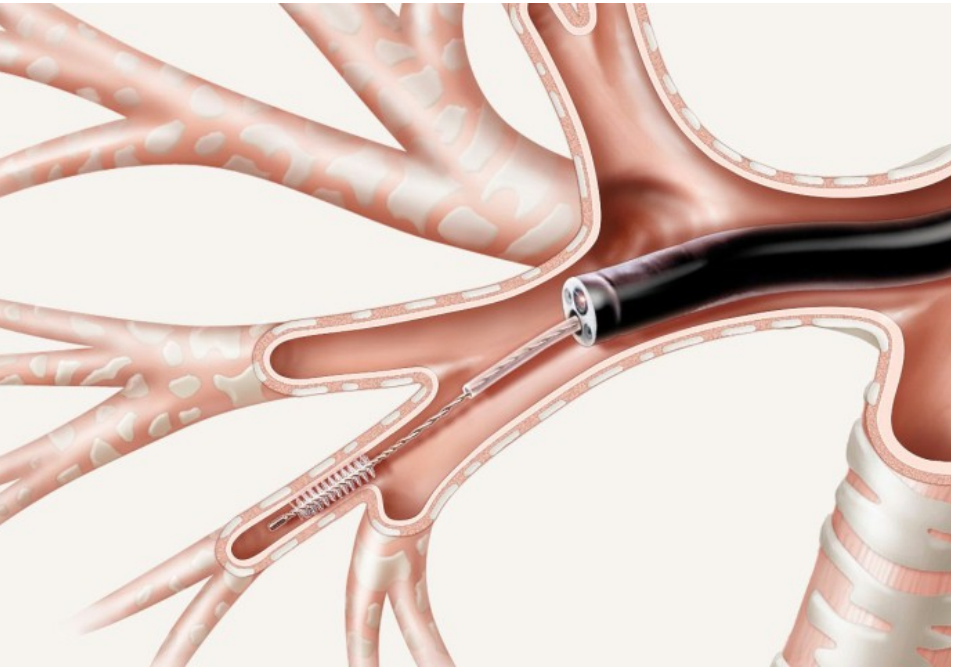




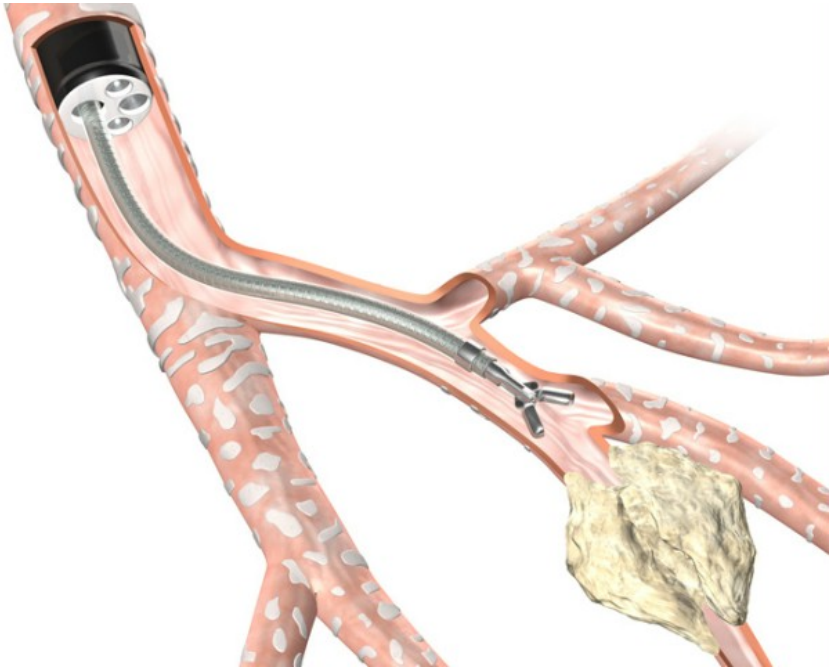


Bile Duct Brushing or Biopsy during ERCP

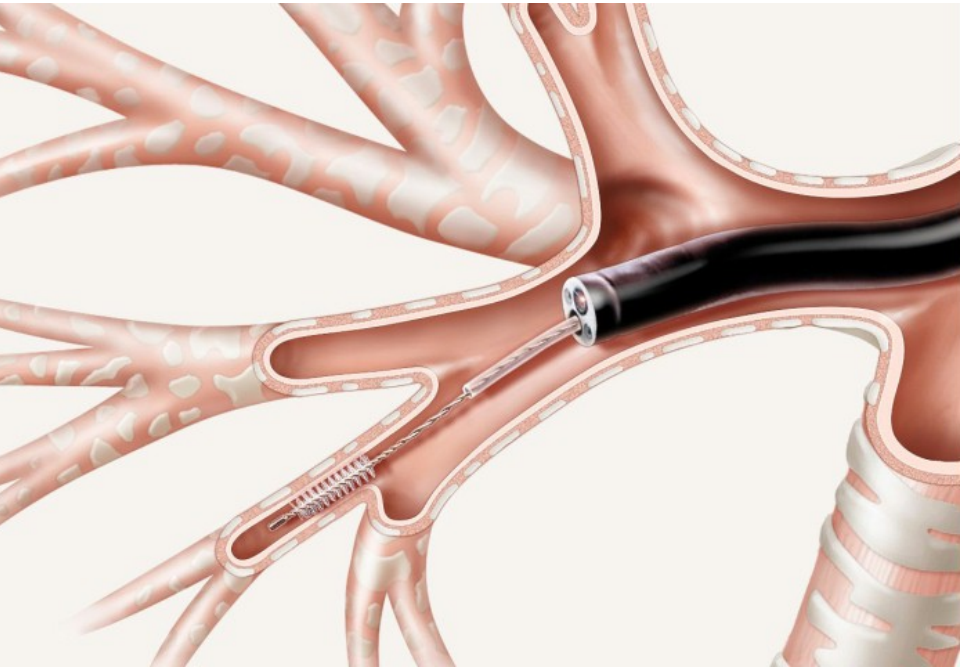
Brushing

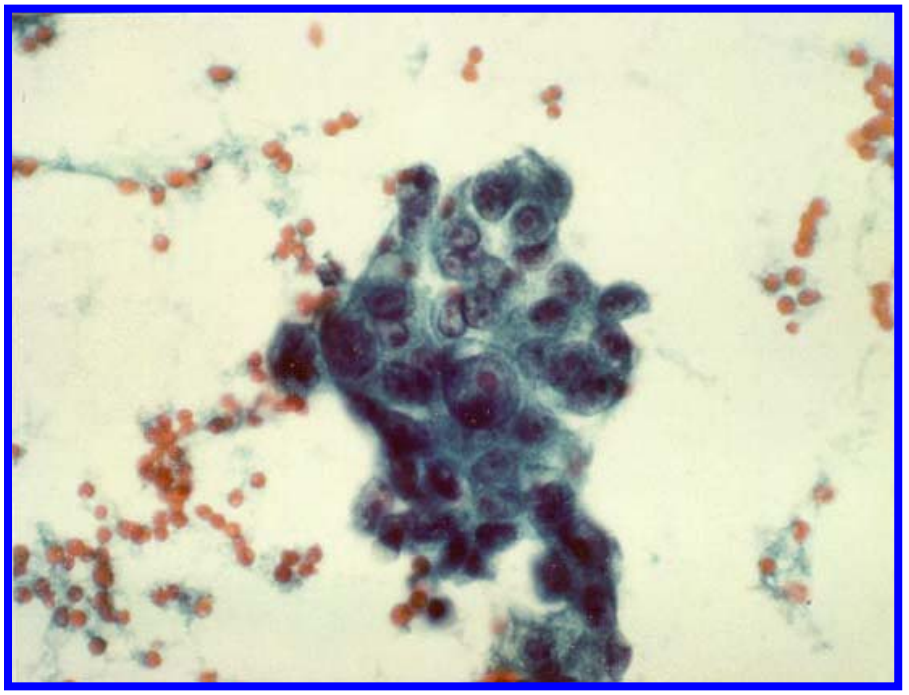


Biopsy



Bile Duct Brushing Samples for Routine Cytology

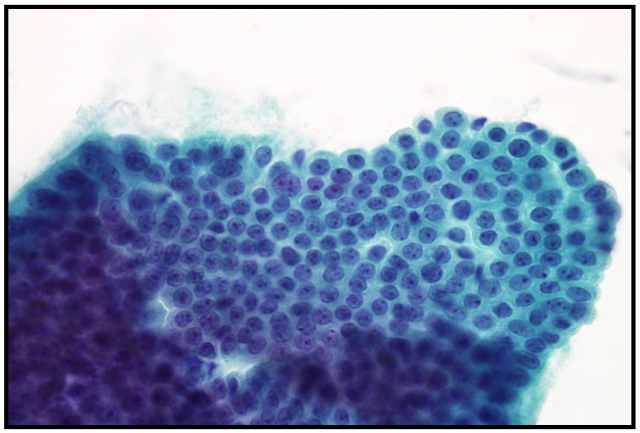




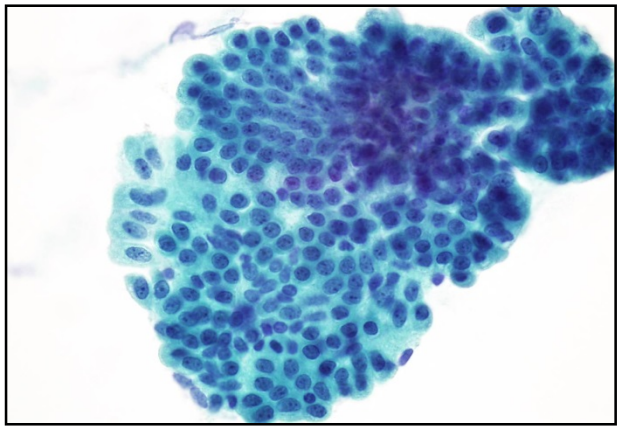
The sensitivity of brush cytology for diagnosis of malignant biliary tract stricture is 15-20%

Image Courtesy of Emily G. Barr Fritcher

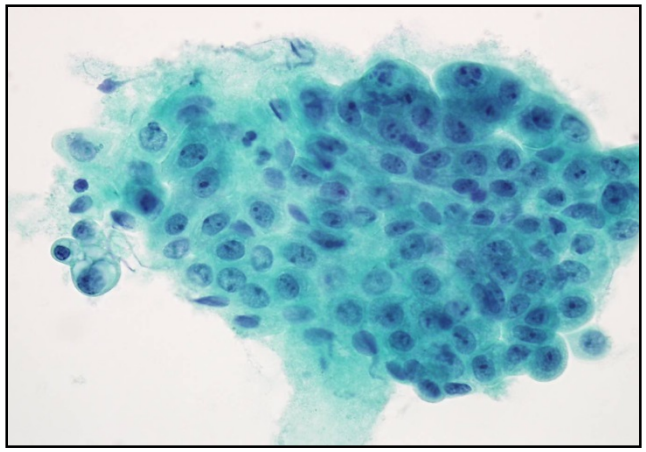
Cytology



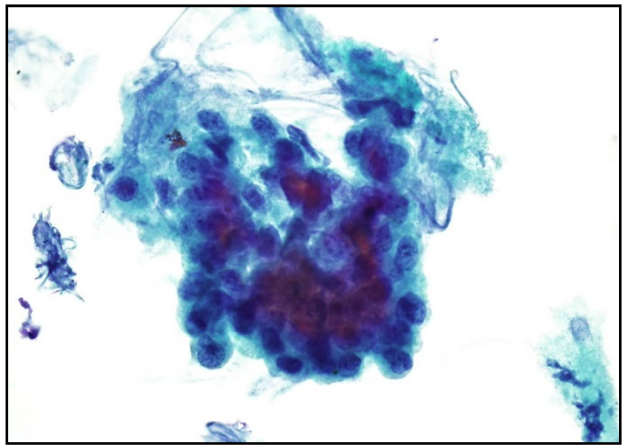
Normal



Atypical



Suspicious



Positive

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Limitations of Cytology

- **Difficult to access and obtain specimens**
- **Cancers are highly desmoplastic**
- **Specimens have very few cells**
- **Diagnostic criteria are subjective**
- **Sensitivity for cancer is only 15-40%**
- **Specificity ~100% - Still a Gold Standard**

Fluorescence In Situ Hybridization (FISH)

- Takes advantage of the genetic aberrations characteristic of cancer
- Aneusomy as a proxy for aneuploidy
- Objective criteria for diagnosis
- Easier identification of abnormal cells
- Established and validated in bladder cancer
- Commercialized by Vysis/Abbott Labs

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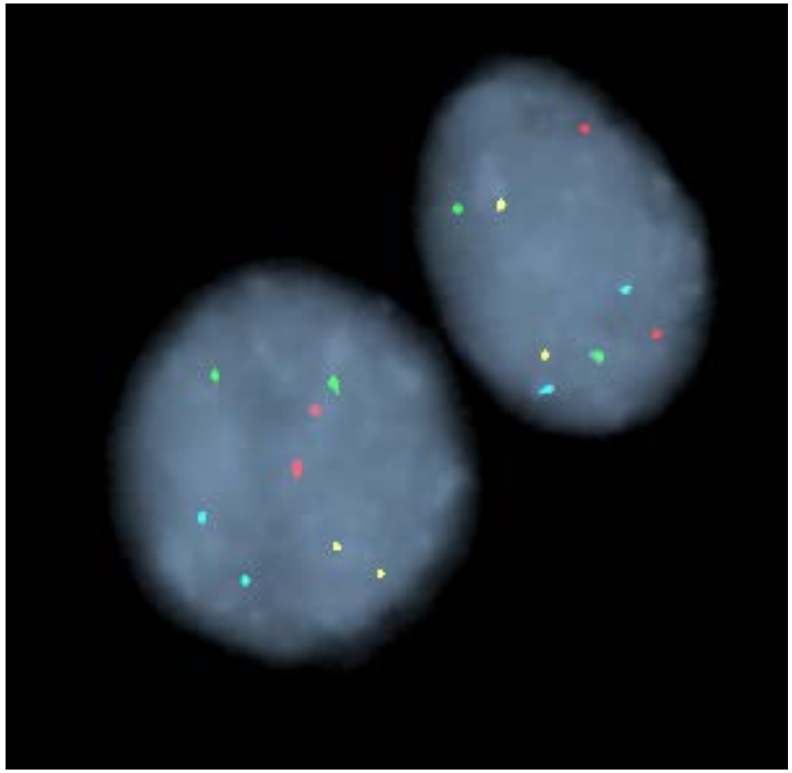
Urovysion FISH Assay

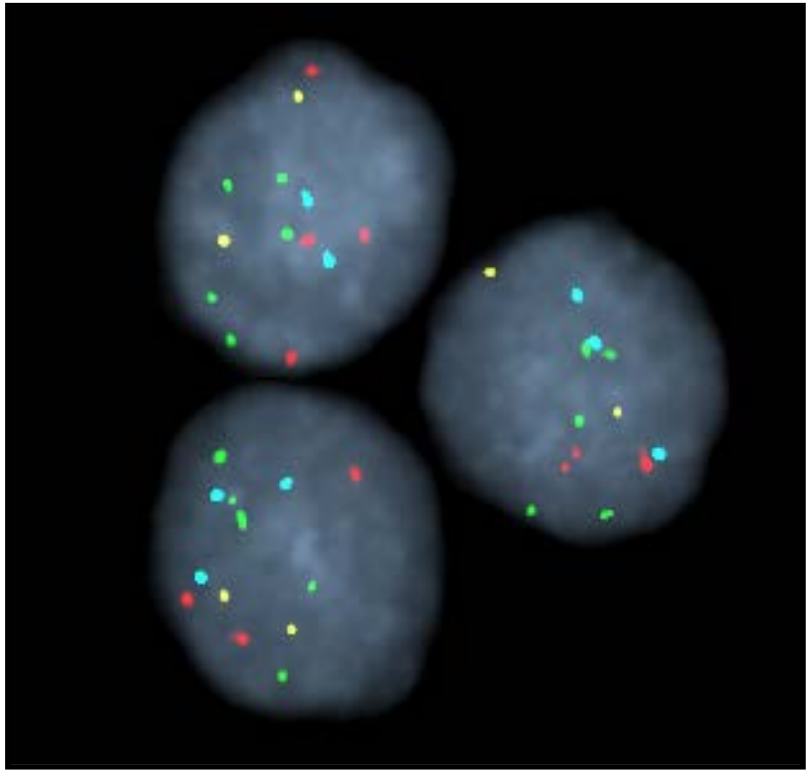
chr 3 = red, chr 7 = green, chr 17 = aqua, locus 9p21 = gold

Normal



2 signals per color

Polysomy



≥ 2 signals in ≥ 2 colors

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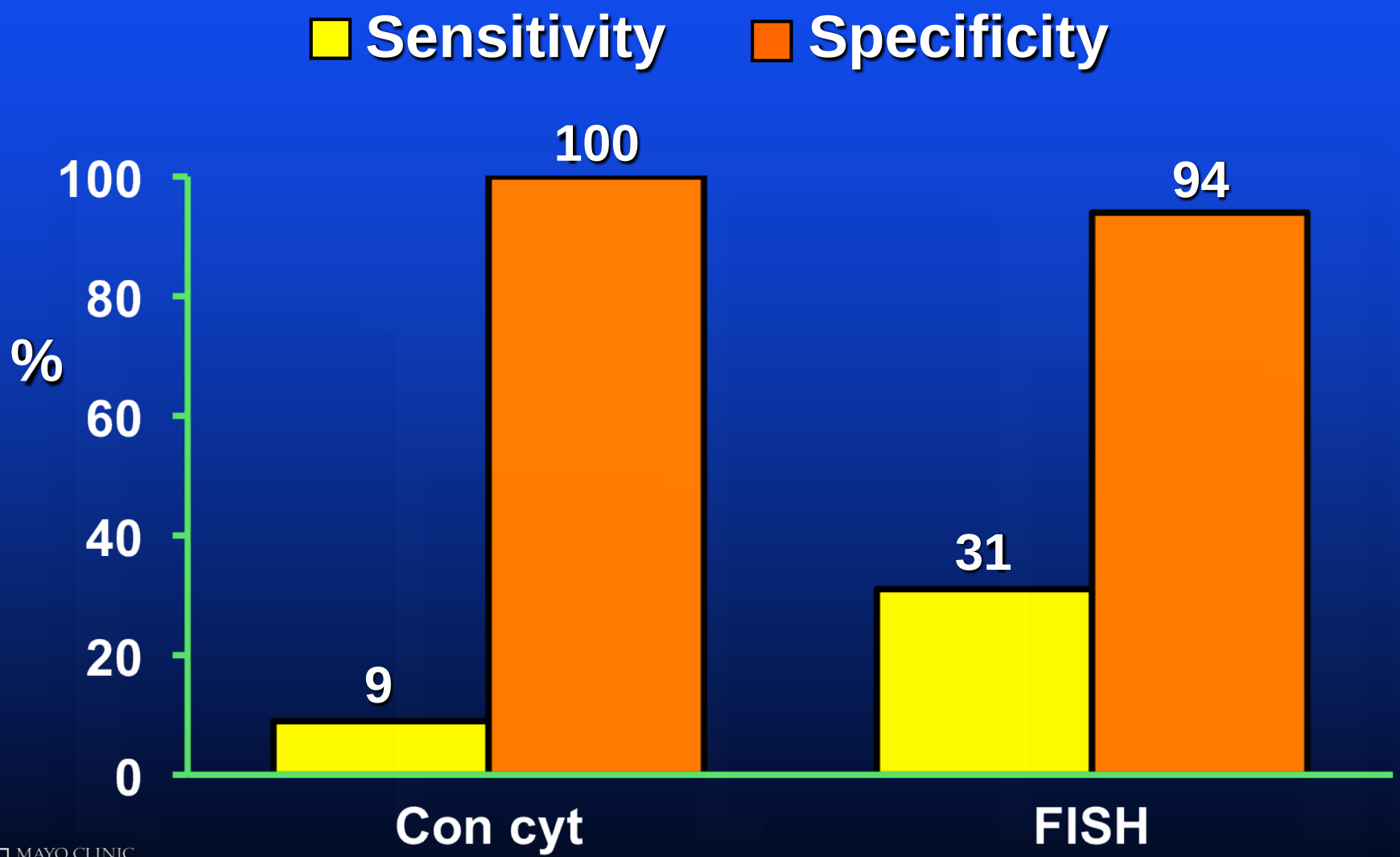
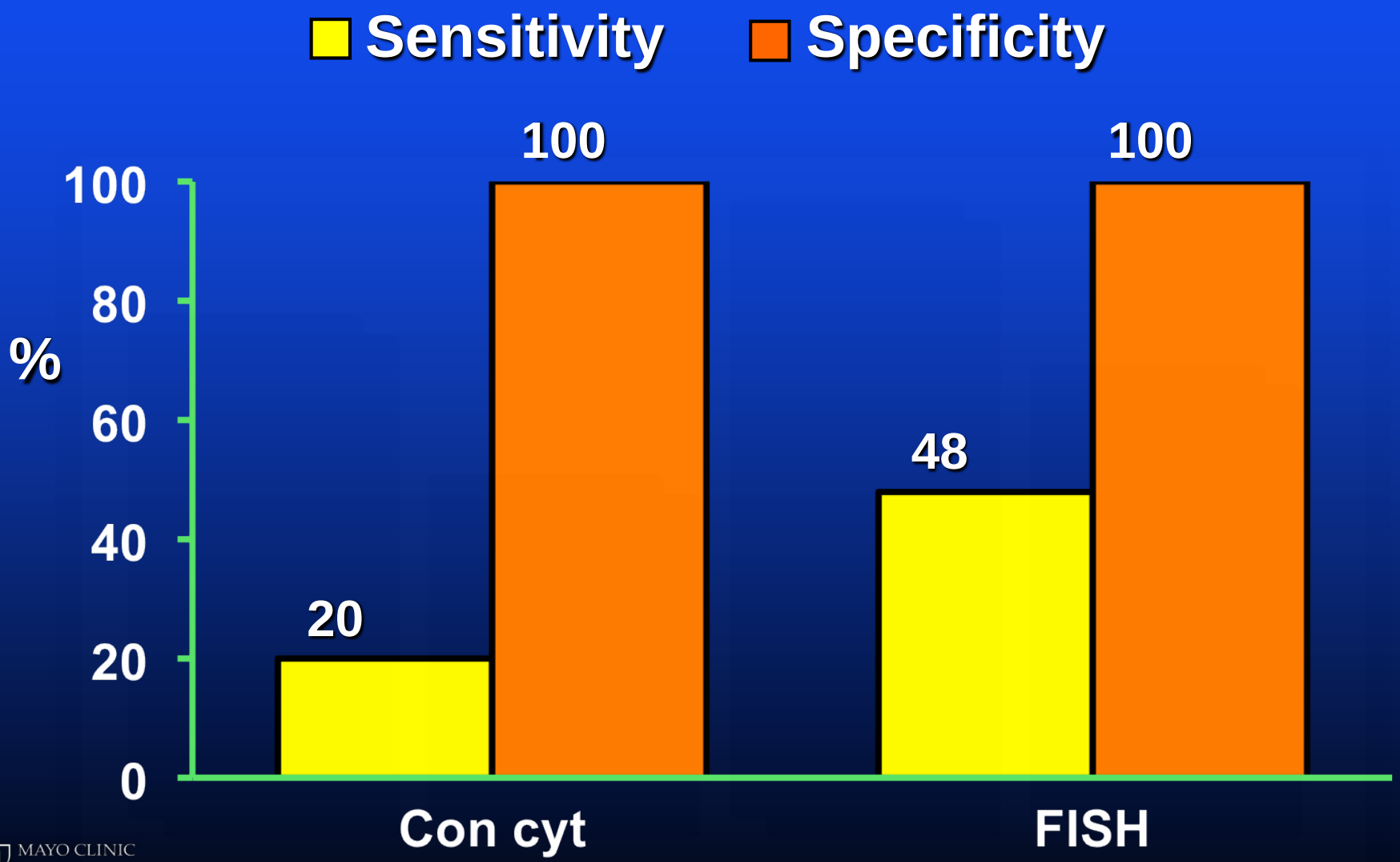
Performance of Cytology versus FISH Polysomy: Proximal Strictures



MAYO CLINIC

Performance of Cytology versus FISH Polysomy: Distal Strictures



A Comparison of Routine Cytology and Fluorescence *in situ* Hybridization for the Detection of Malignant Bile Duct Strictures

Benjamin R. Kipp, Linda M. Stadheim, Shari A. Halling, Nicole L. Pochron, Scott Harmsen, David M. Nagorney, Thomas J. Sebo, Terry M. Therneau, Gregory J. Gores, Piet C. de Groen, Todd H. Baron, Michael J. Levy, Kevin C. Halling, and Lewis R. Roberts

Advanced Cytologic Techniques for the Detection of Malignant Pancreatobiliary Strictures

LAURA E. MORENO LUNA,* BENJAMIN KIPP,‡ KEVIN C. HALLING,‡ THOMAS J. SEBO,‡ WALTER K. KREMERS,§ LEWIS R. ROBERTS,* EMILY G. BARR FRITCHER,‡ MICHAEL J. LEVY,* and GREGORY J. GORES*

A Multivariable Model Using Advanced Cytologic Methods for the Evaluation of Indeterminate Pancreatobiliary Strictures

EMILY G. BARR FRITCHER,* BENJAMIN R. KIPP,* KEVIN C. HALLING,* TRYNDA N. OBERG,* SANDRA C. BRYANT,‡ ROBERT F. TARRELL,‡ GREGORY J. GORES,‖ MICHAEL J. LEVY,‖ AMY C. CLAYTON,* THOMAS J. SEBO,* and LEWIS R. ROBERTS‖

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Outcome

- **The UroVysion™ FISH assay is now widely used in the U.S. and Europe as an ancillary diagnostic tool for evaluating biliary strictures**
- **FISH has also been validated for diagnosis of biliary strictures in Asia**

Fluorescence in situ hybridization compared with conventional cytology for the diagnosis of malignant biliary tract strictures in Asian patients

Roongruedee Chaiteerakij, MD, PhD,[1,3] Emily G. Barr Fritcher, CT (ASCP),[2] Phonthep Angsuwatcharakon, MD,[3] Wiriyaporn Ridtitid, MD,[3] Supakarn Chaithongrat, BSc,[3] Apinya Leerapun, MD,[4] Todd H. Baron, MD,[1,5] Benjamin R. Kipp, PhD,[2] Michael R. Henry, MD,[2] Kevin C. Halling, MD, PhD,[2] Rungsun Rerknimitr, MD,[3]* Lewis R. Roberts, MBChB, PhD[1,*]

Rochester, Minnesota, USA; Bangkok, Chiang Mai, Thailand; Chapel Hill, North Carolina, USA

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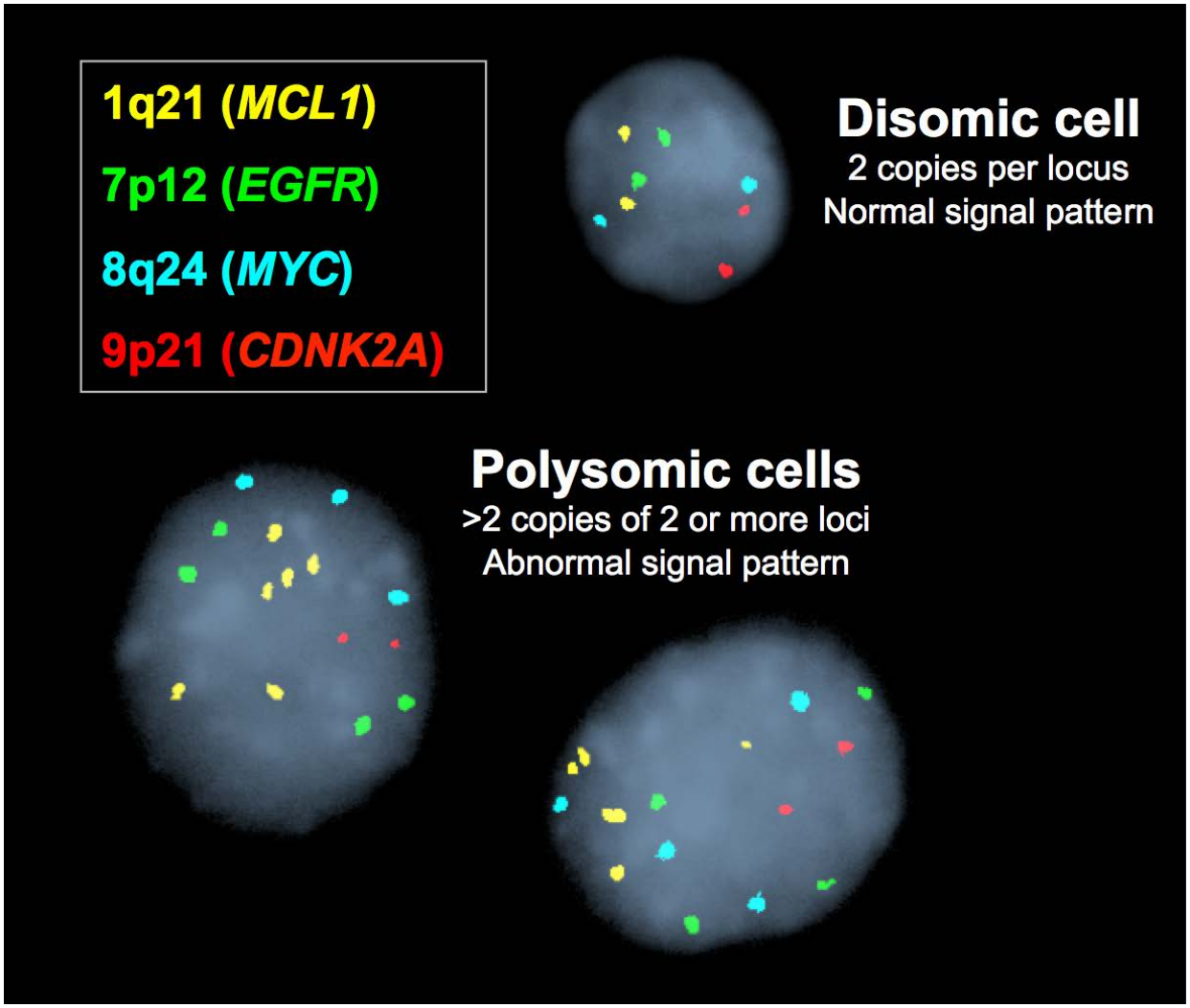
Development of a Tailored Pancreatobiliary FISH Assay



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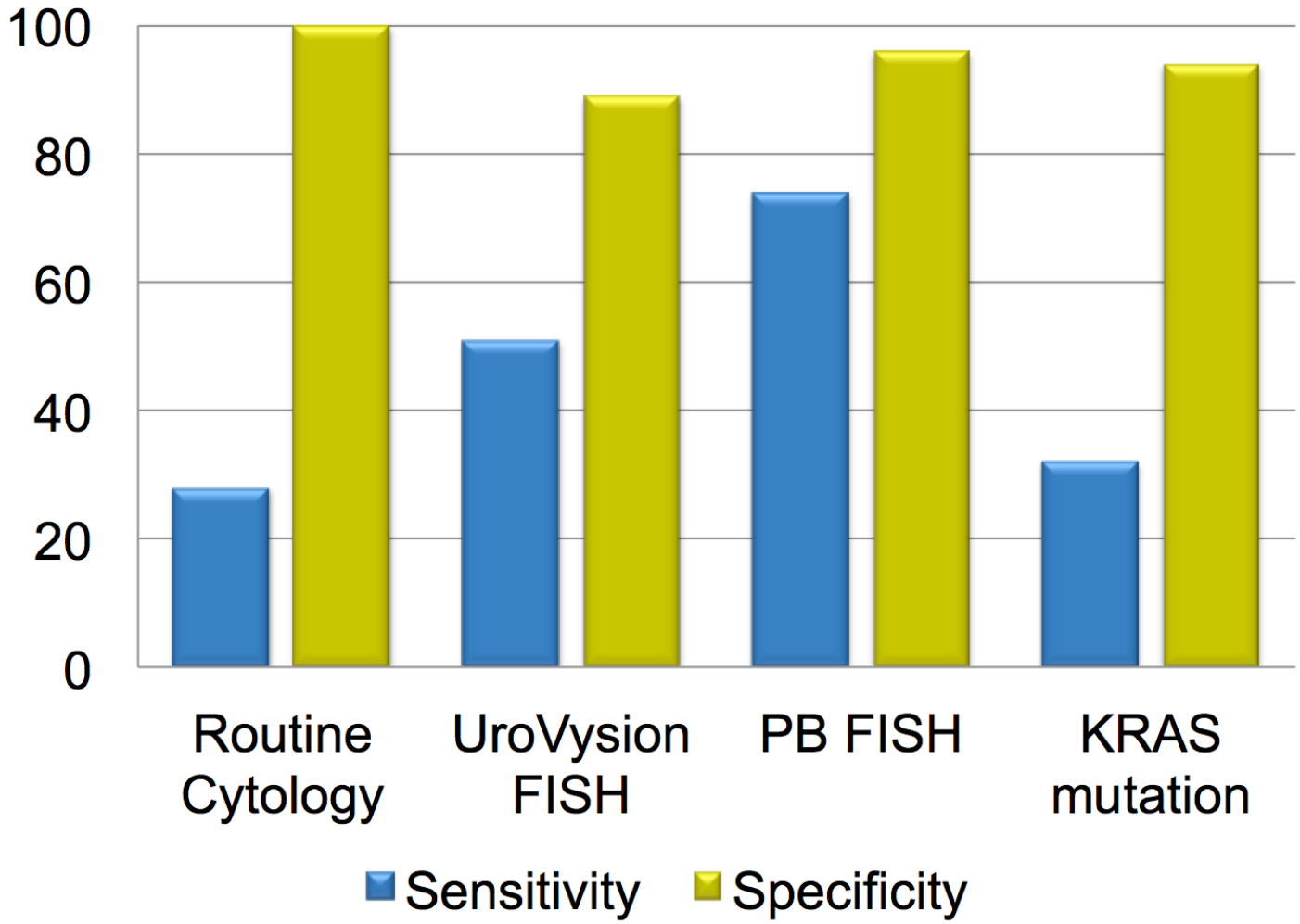
Improved Performance of PB-FISH Assay: A New Standard



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Outline

- My Story – The village raised this child
- Hepatitis B Virus Integrations in Liver Cancer
- Fluorescence In Situ Hybridization for Diagnosis of Pancreatobiliary Cancer
- **The Global HCC BRIDGE Study**
- The Cancer Genome Atlas Projects for Liver and Biliary Cancer
- Global – This is no time for small dreams

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Global Patterns of Hepatocellular Carcinoma Management from Diagnosis to Death: the BRIDGE Study

Joong-Won Park[1], Minshan Chen[2], Massimo Colombo[3], Lewis R. Roberts[4], Myron Schwartz[5], Pei-Jer Chen[6], Masatoshi Kudo[7], Philip Johnson[8], Samuel Wagner[9], Lucinda S. Orsini[10], Morris Sherman[11]

[1]Center for Liver Cancer, National Cancer Center, Goyang, Republic of Korea, [2]Sun Yat-Sen University Cancer Center, Guangzhou, People's Republic of China, [3]Policlinic IRCCS Maggiore Hospital,University of Milan, Italy, [4]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA, [5]Mount Sinai Hospital, New York, NY, USA, [6]Taiwan National University, Taipei, Taiwan, [7]Kinki University School of Medicine, Osaka-Sayama, Osaka, Japan, [8]Birmingham University, Birmingham, UK, [9]Bristol-Myers Squibb, Princeton, NJ, USA, [10]Bristol-Myers Squibb, Wallingford, CT, USA, [11]University of Toronto, Toronto, Ontario, Canada

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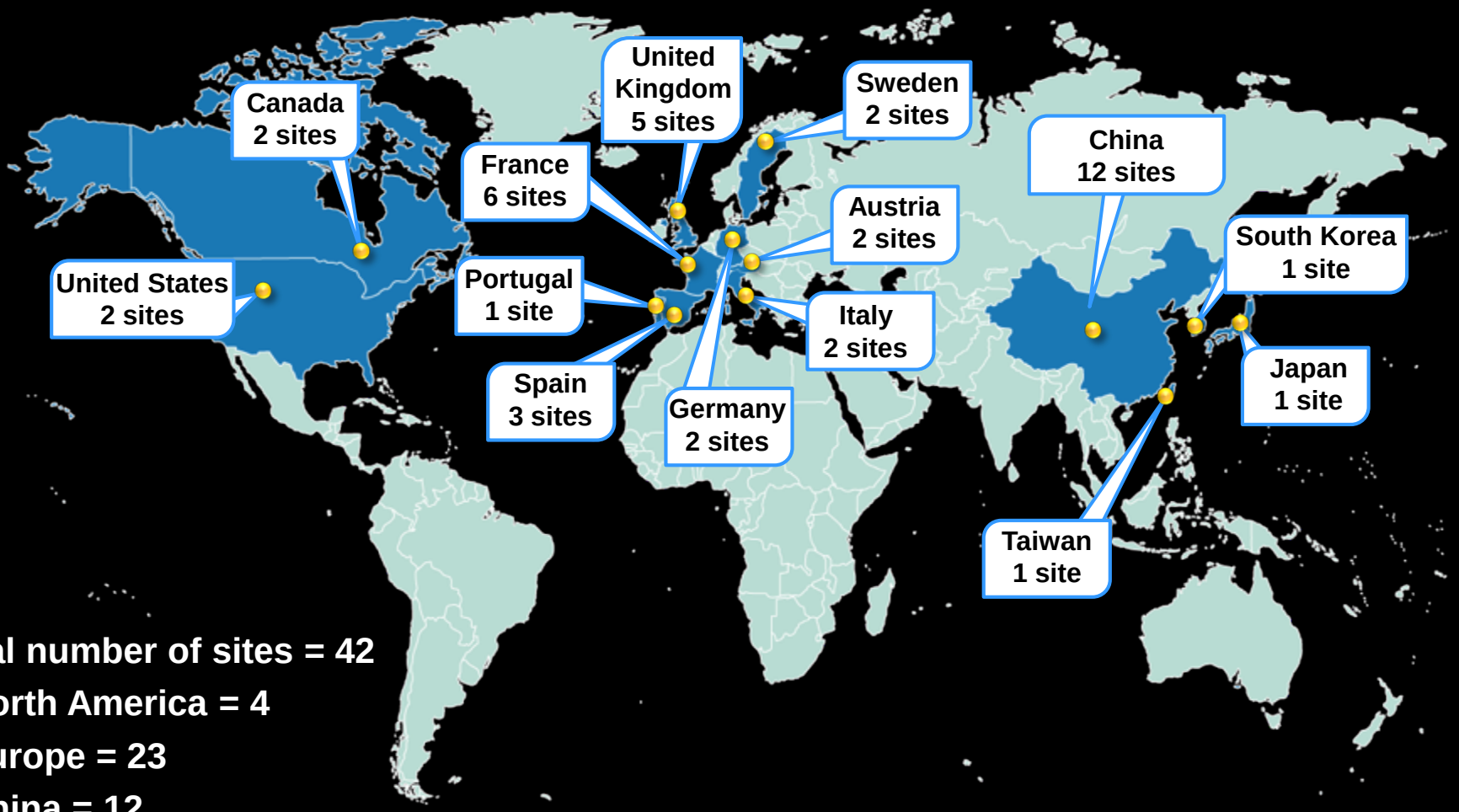
Park et al., Liver International 2015

BRIDGE Study Design

- The global HCC BRIDGE study ("Bridge to Better Outcomes in HCC") was the first multi-regional, large-scale observational study to document HCC patient experience from diagnosis to death
- Designed to improve our understanding of global patterns of HCC therapy and associated outcomes in real-world clinical practice
- Included all patients who received treatment for HCC, regardless of treatment type
- Included patients treated for HCC in 3 major regions: Asia-Pacific, Europe, and North America

Park et al., Liver International 2015, In Press

42 Participating Sites

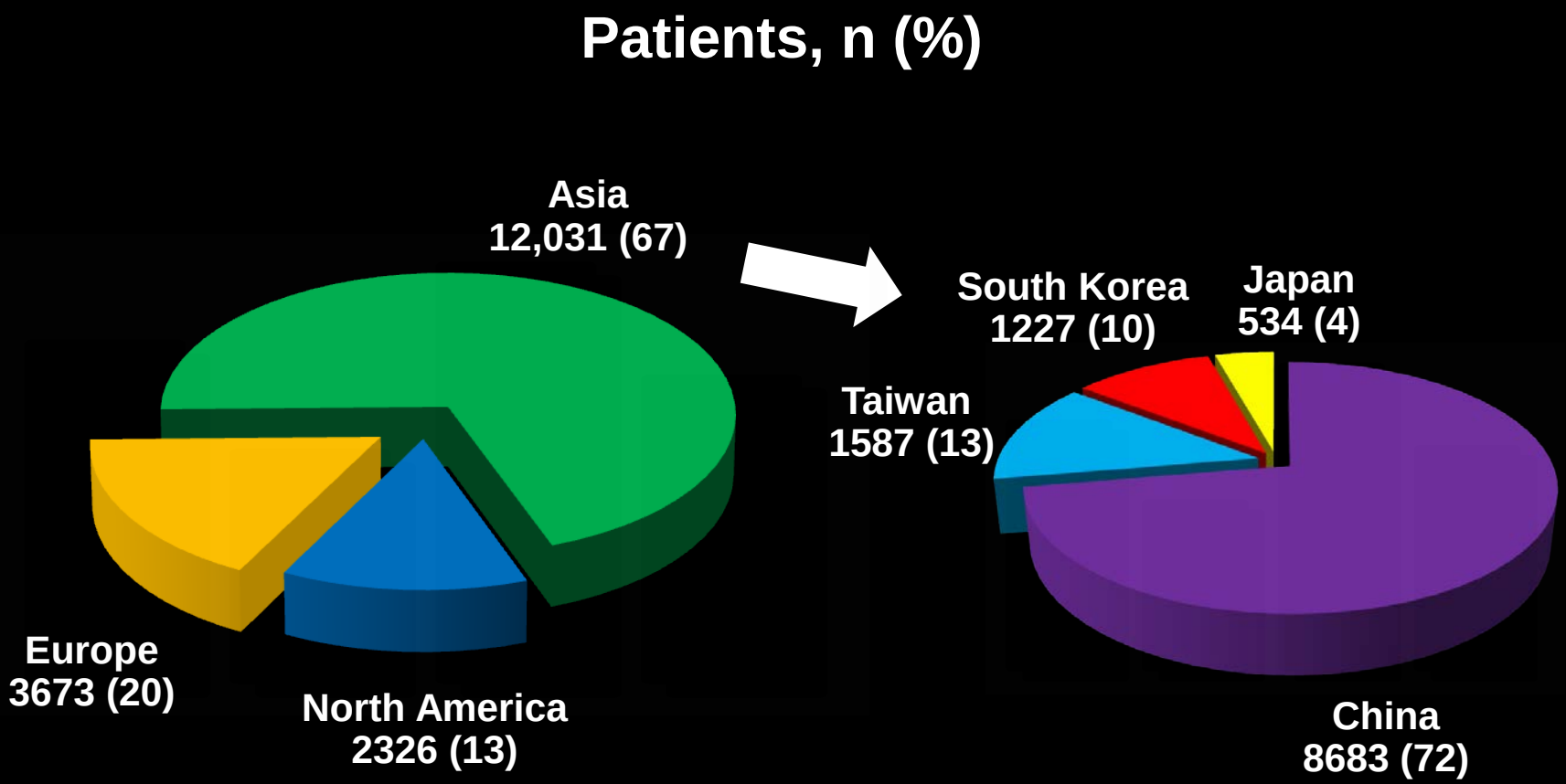


Total number of sites = 42

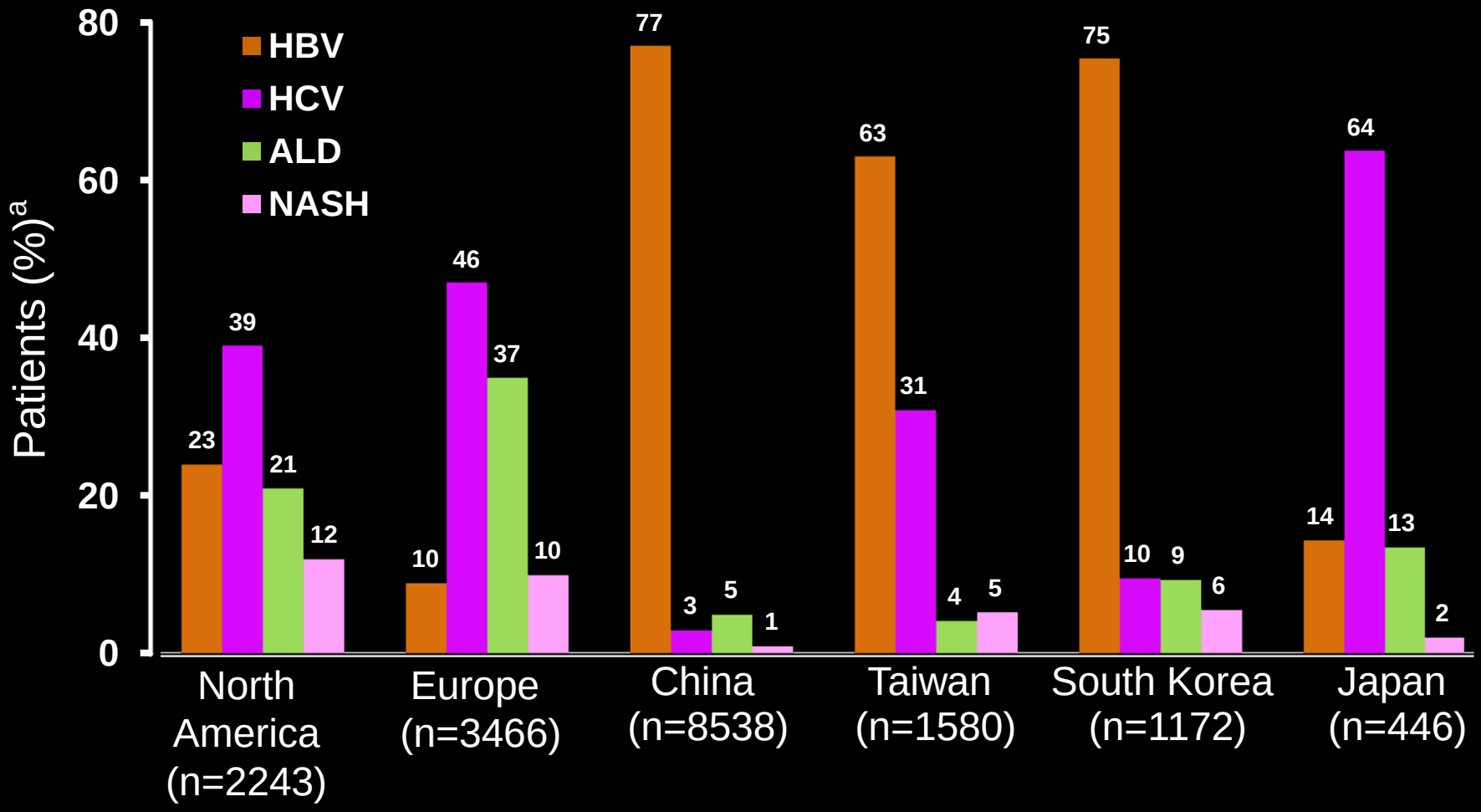
- **North America = 4**
- **Europe = 23**
- **China = 12**
- **Taiwan = 1**
- **South Korea = 1**
- **Japan = 1**

Park et al., Liver International 2015, In Press

Patients Treated for HCC by Region (N = 18,030)



There is Significant Geographic Variation in HCC Risk Factors (N = 17,445)



[a]Percentages are based on percent of population with known values.
ALD, alcoholic liver disease; NASH, non-alcoholic steatohepatitis.

Park et al., Liver International 2015

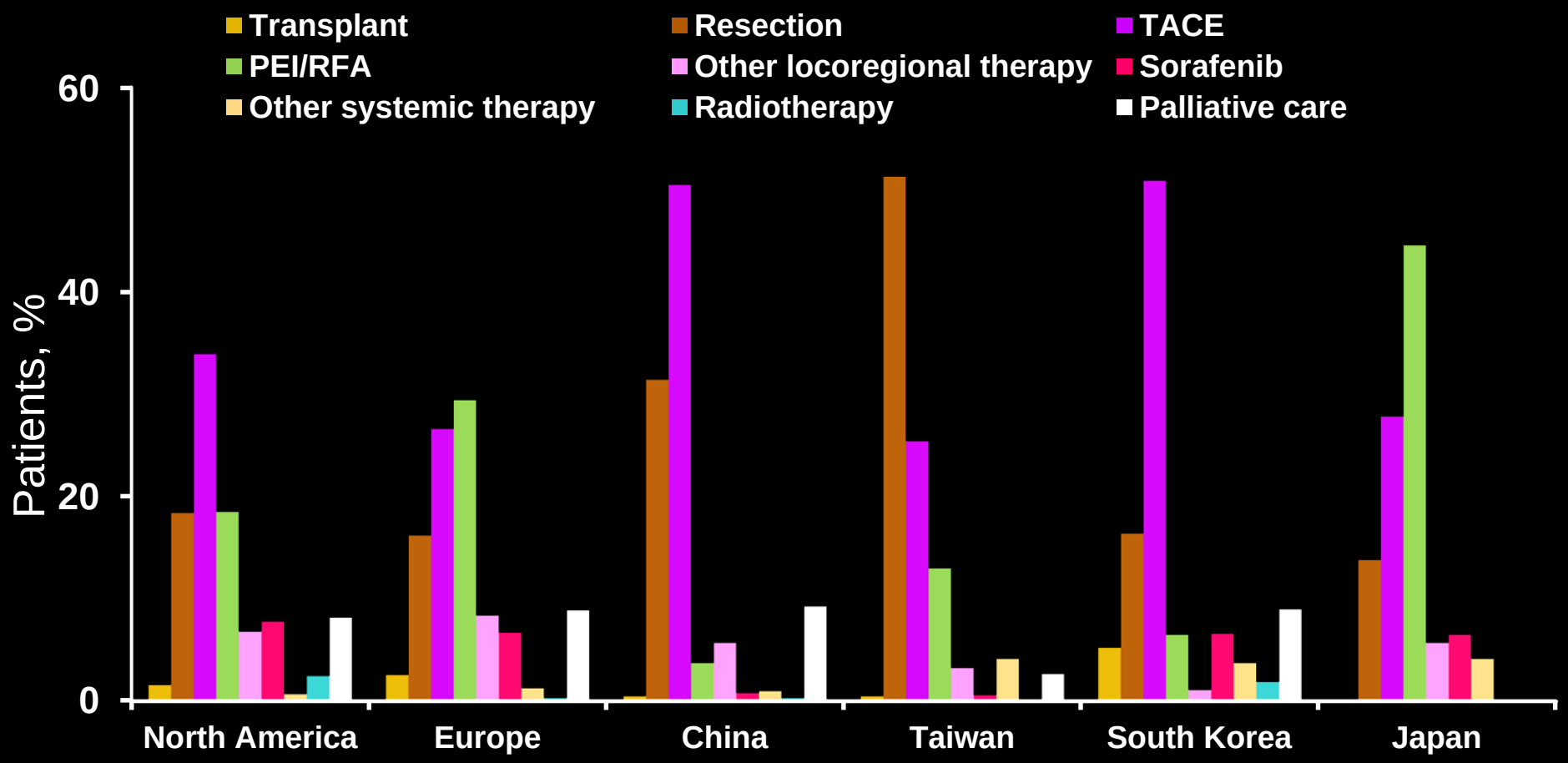
HCC is Diagnosed at More Advanced Stages in Most Countries, except Taiwan and Japan

Variable	North America n = 2326	Europe n = 3673	China n = 8683	Taiwan n = 1587	South Korea n = 1227	Japan n = 534
BCLC stage, n (%)	n = 1588	n = 2261	n = 6501	n = 1461	n = 1152	n = 433
0	107 (7)	84 (4)	192 (3)	213 (15)	82 (7)	107 (25)
A	474 (30)	582 (26)	1973 (30)	810 (55)	290 (25)	206 (48)
B	157 (10)	253 (11)	591 (9)	176 (12)	149 (13)	62 (14)
C	673 (42)	1158 (51)	3606 (56)	250 (17)	605 (53)	53 (12)
D	177 (11)	184 (8)	139 (2)	12 (1)	26 (2)	5 (1)

[a]Statistics based on patients with known values.
BCLC, Barcelona Clinic Liver Cancer.

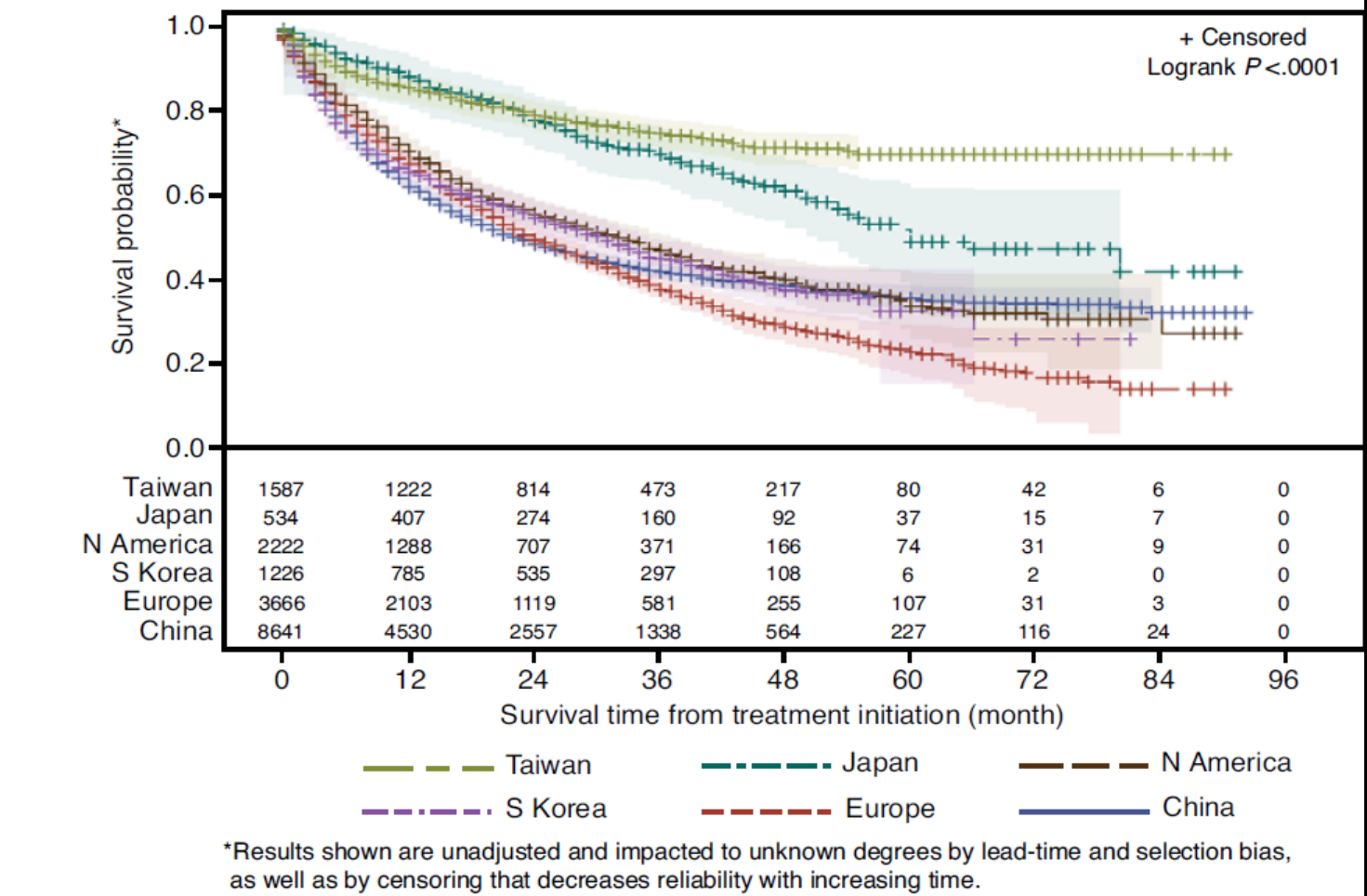
Park et al., Liver International 2015

The First Recorded HCC Treatment Also Varies by Country and Region



Kudo et al., APPLE 2012

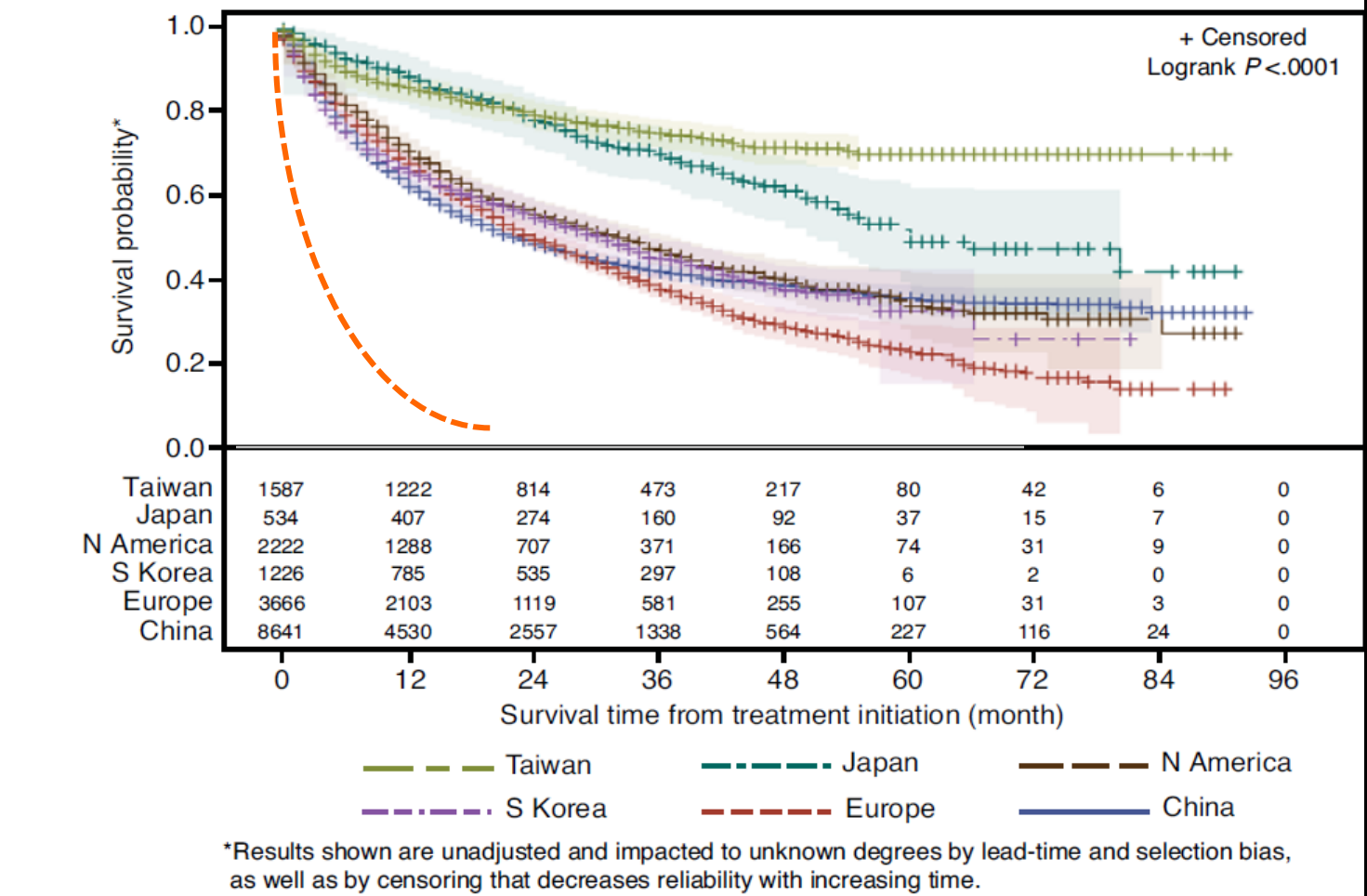
Surveillance Determines Median Overall Survival



- Median OS was not reached for Taiwan and was 60 mo for Japan
- Median OS was 33 mo for North America, 31 mo for South Korea, 24 mo for Europe, and 23 mo for China.

Park et al., Liver International 2015

Africa has the Worst Estimated Median Survival



- Median OS was not reached for Taiwan and was 60 mo for Japan
- Median OS was 33 mo for North America, 31 mo for South Korea, 24 mo for Europe, and 23 mo for China. Estimated median survival in Africa is 3 mo.

Park et al., Liver International 2015

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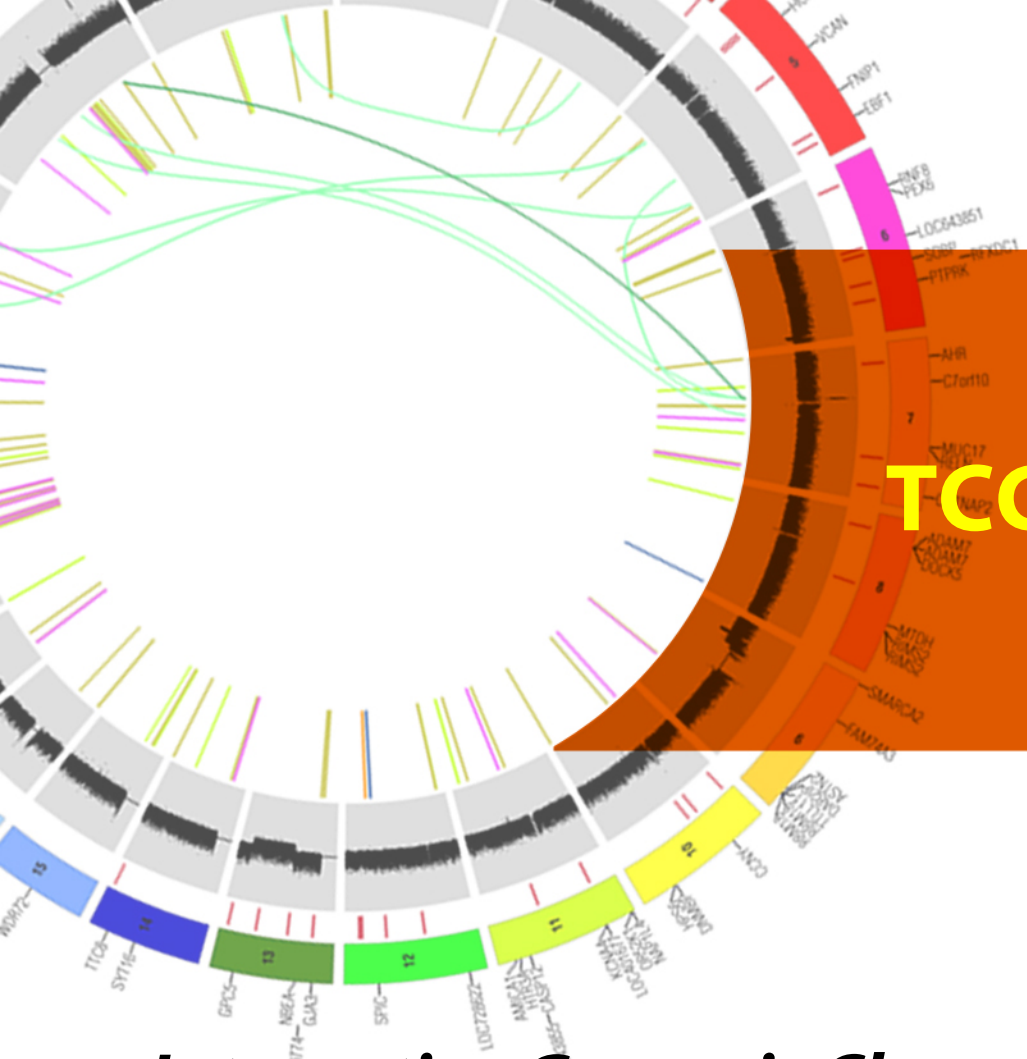


The Cancer Genome Atlas

TCGA HCC Update

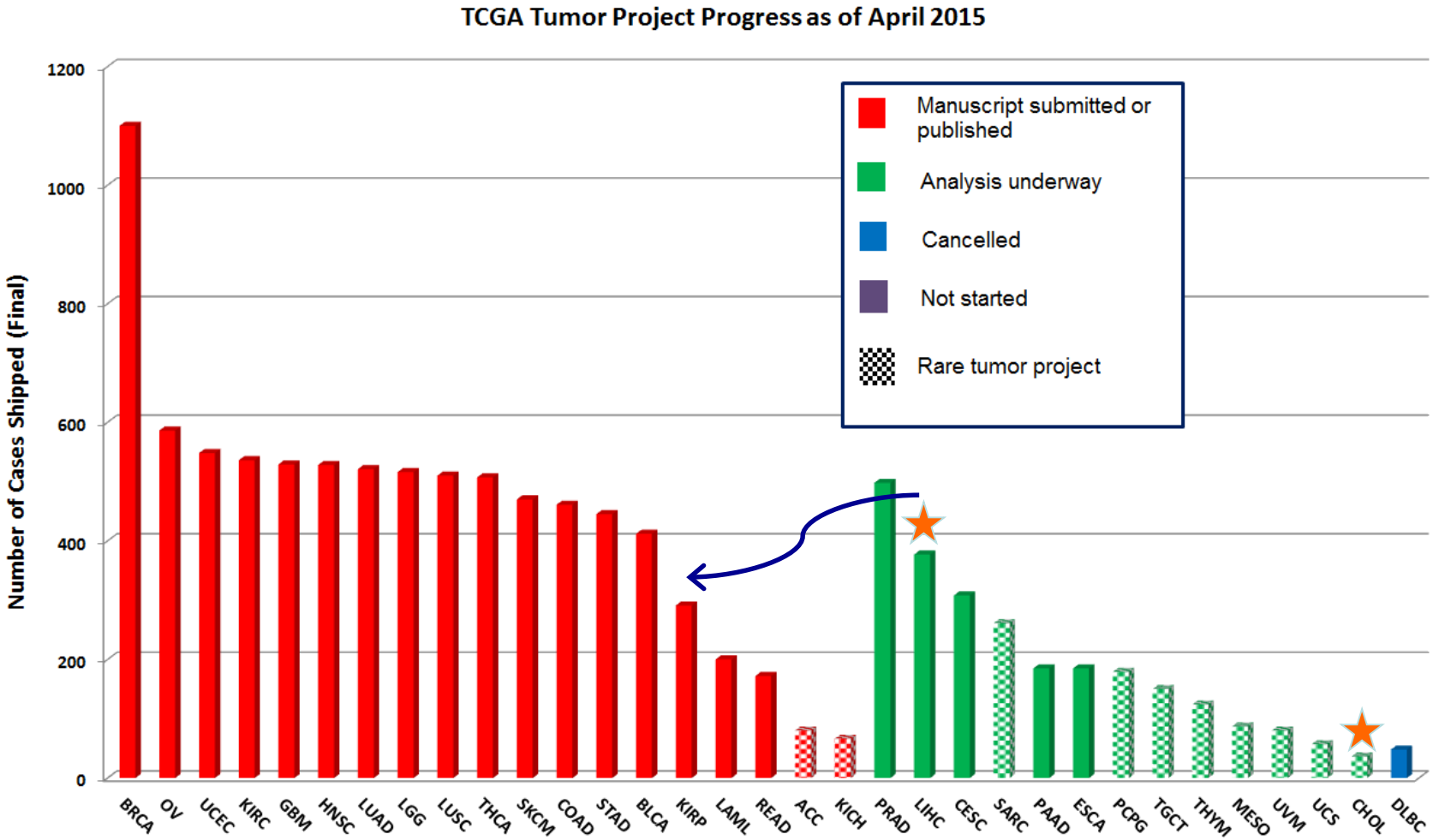
Integrative Genomic Characterization of HCC by The Cancer Genome Atlas Project:

Team Science, Translational Potential, and the New Cancer Genomics Cloud Pilots

Goals of TCGA (2006-2016)

- To accelerate our understanding of the molecular basis of cancer through the application of genome analysis technologies to 500 cases of each of 25 cancers
- Comprehensive genetic, genomic and proteomic analysis of major cancer types and rare cancers
- Pan-Cancer Analysis of Whole Genomes
- Stimulate applications of cancer genomics in medicine
- Data broadly available to the cancer research community (http://cancergenome.nih.gov/)
- Over 2,100 publications referencing TCGA to date

TCGA Tumor Project Progress



TCGA HCC Project and Platforms

- Whole genome sequencing of 50 HCCs
- Whole exome sequencing of ~377 HCCs with multi-center mutation calling; initial analysis of 196 HCCs
- TERT promoter mutation sequencing
- Somatic copy number analysis
- 450K Illumina Whole Genome DNA Methylation
- RNA sequencing
- miRNA sequencing
- Reverse Phase Protein Array

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Lack of Data and Inaccurate Data Have Important Effects on Global Health Policy

Promoting the Birth Dose of Hepatitis B vaccination – GAVI responds to MSF

"WHO estimates that hepatitis B causes around 260,000 deaths each year in GAVI-eligible countries, mostly in older men."

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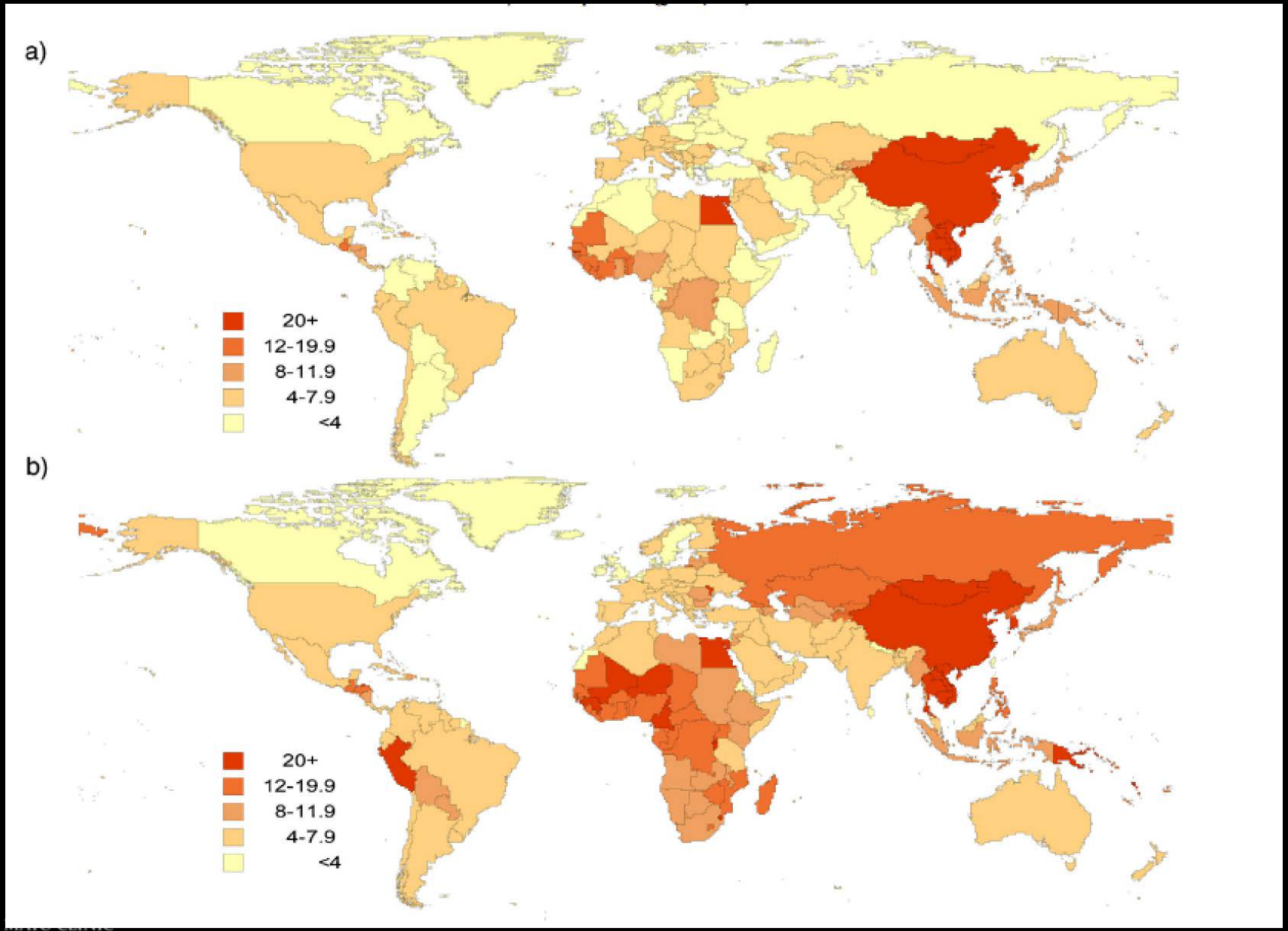
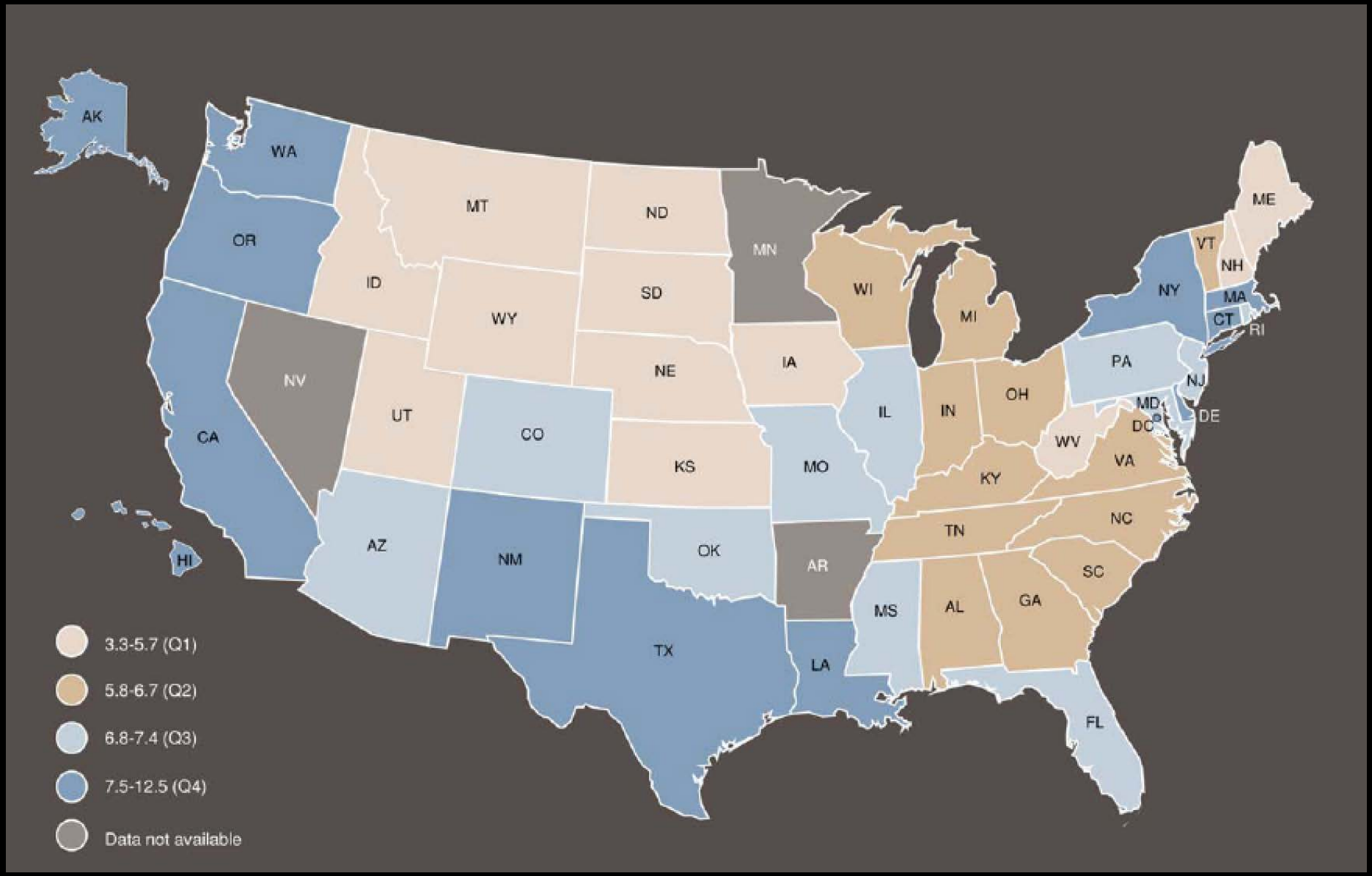
HCC is Underestimated Globally



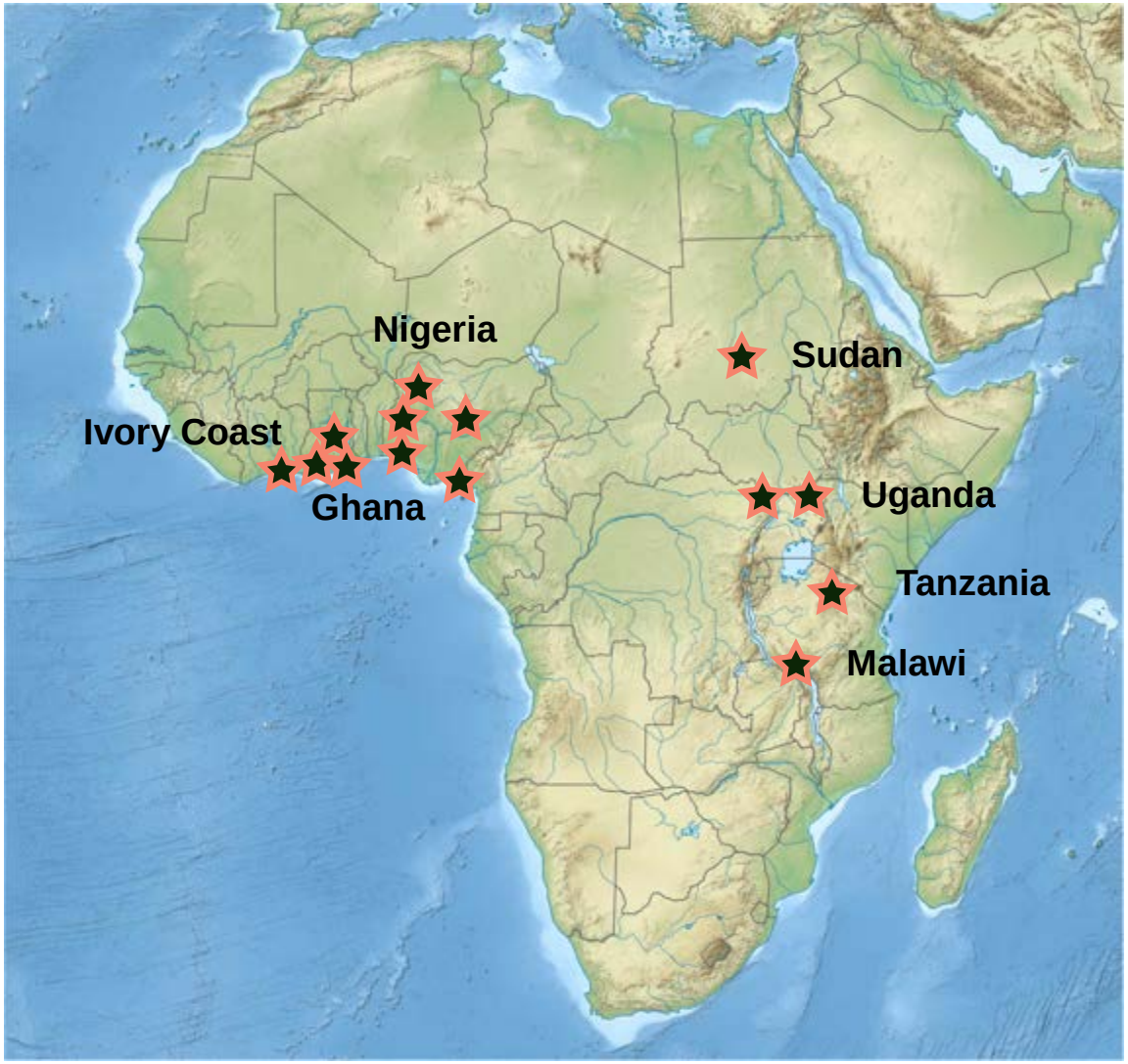
Sartorius et al, 2015

Some US States are High HCC Incidence



Ryerson et al, 2016

Africa Network for GI and Liver Diseases HCC Study



Yang, DDW Presentation 2015

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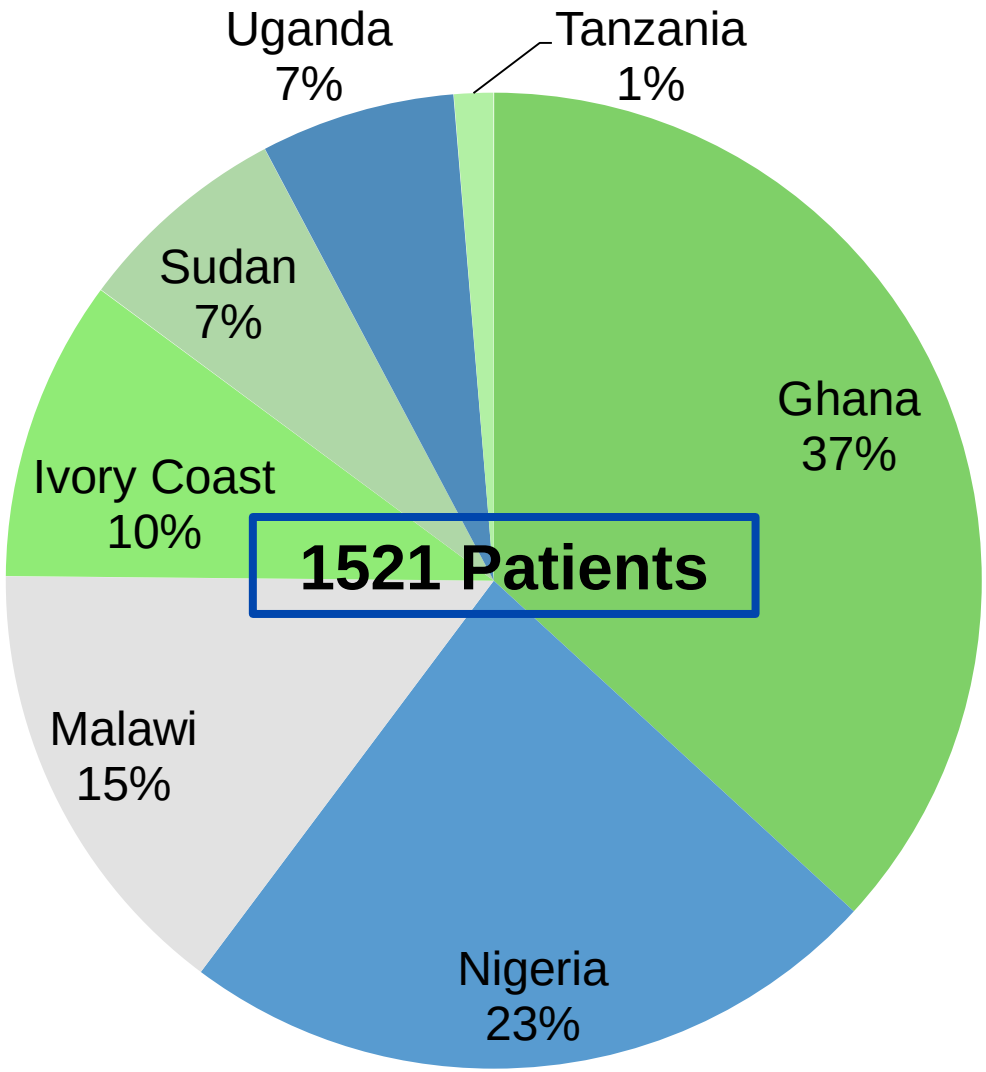
Africa Network for GI and Liver Diseases HCC Study



Yang, DDW Presentation 2015

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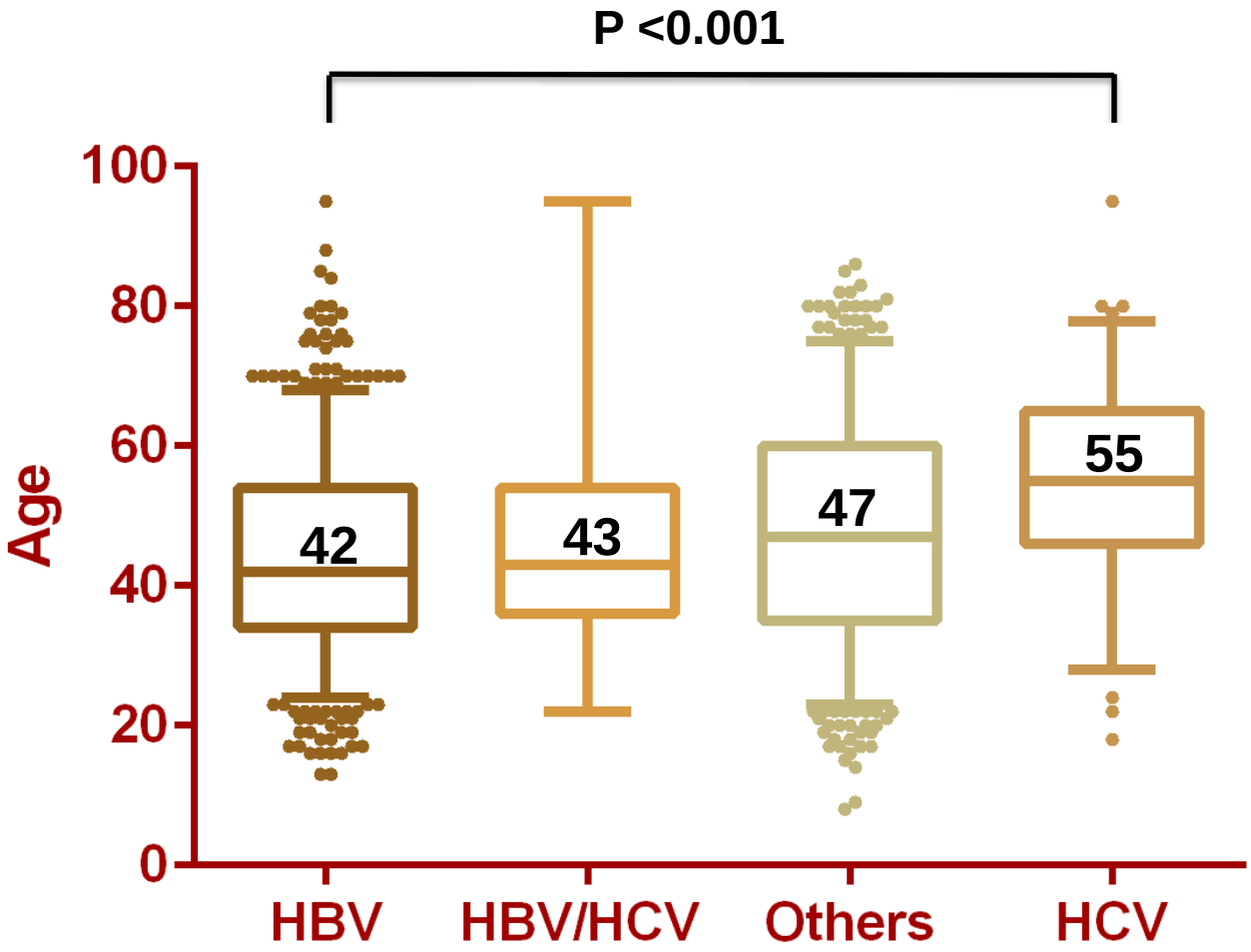
HBV is Associated with Earlier Age of Onset of HCC



Yang, DDW Presentation 2015

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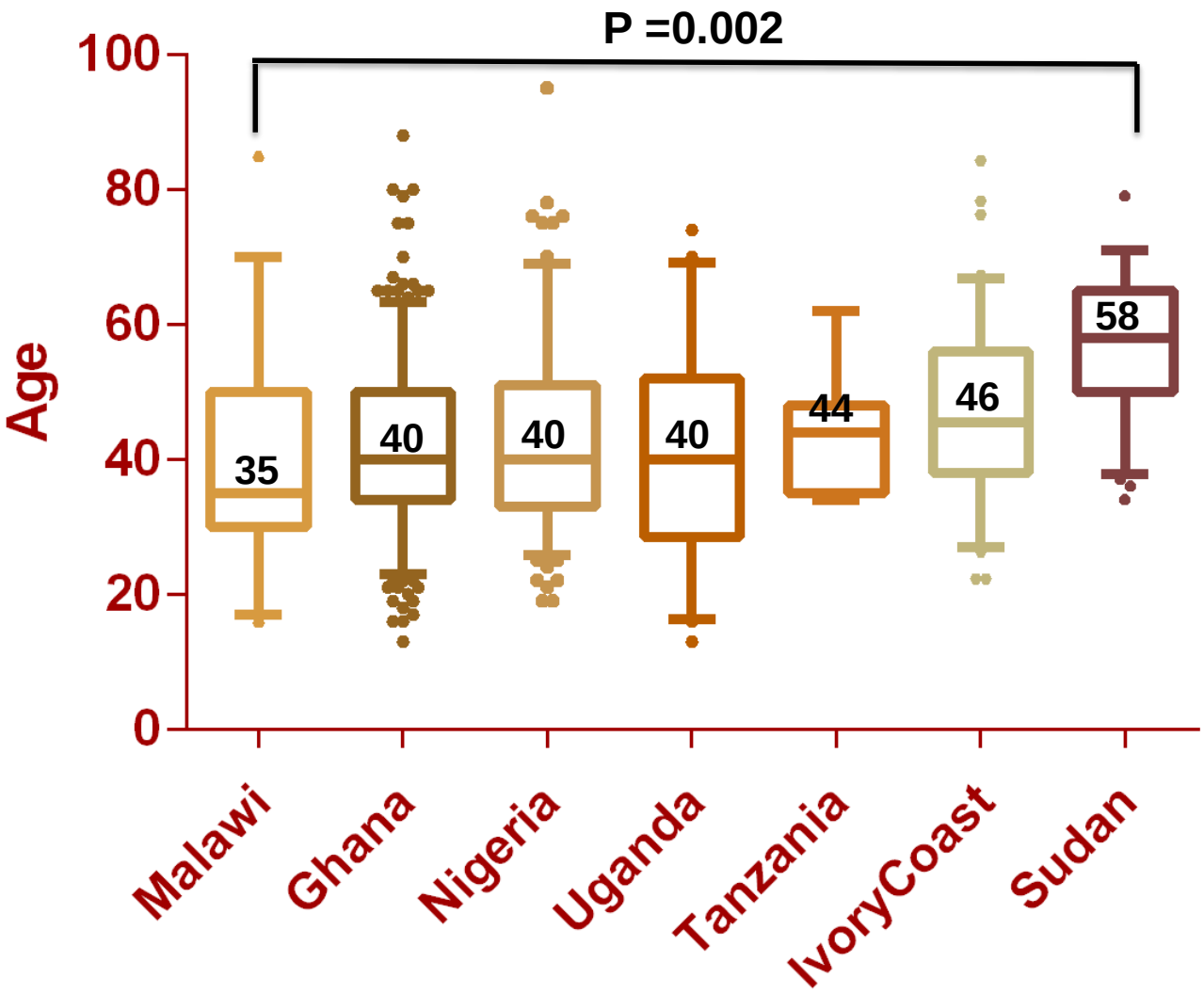
Substantial Variation in Age of Onset of HBV Associated HCC by Country

Median age:
45 [35-58]



Yang, DDW Presentation 2015

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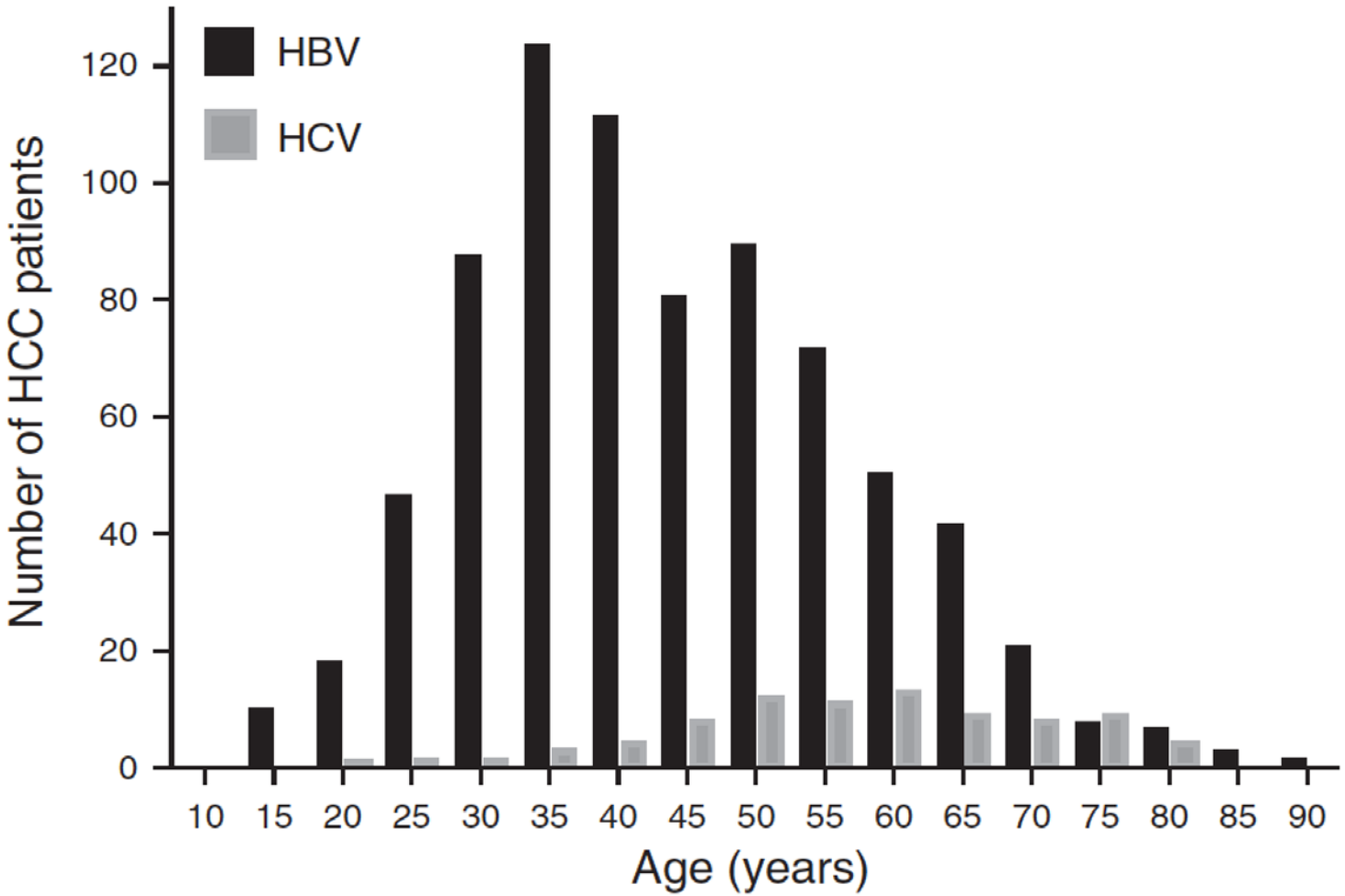
The Peak Age of HBV Associated HCC in Africa is 35-40 Years of Age



Yang et al., Am. J Gasro 2015, In Press

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Summary Thoughts

“In God we trust, everyone else must bring data.” W. Edwards Deming

Recommended Reading:

Concepts of Total Quality Management

Scrum: The Art of Doing Twice the Work in Half the Time. Jeff Sutherland

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Thank You!