Tumor Based Screening for Lynch Syndrome

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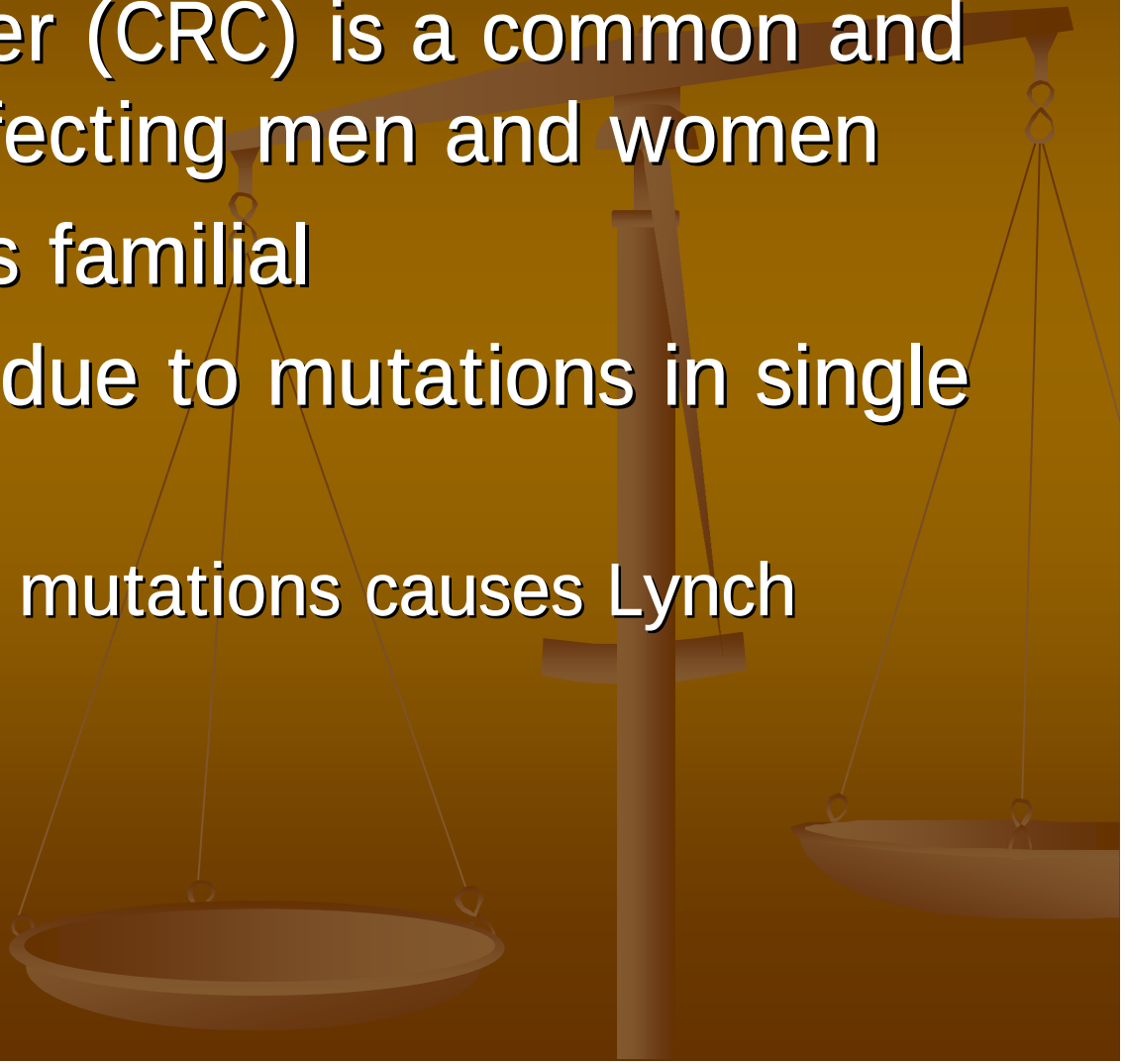
Colorectal Cancer

- Colorectal Cancer (CRC) is a common and lethal cancer affecting men and women
- 5-10% of CRC is familial
- 1-5% of CRC is due to mutations in single genes
  - Subset of these mutations causes Lynch syndrome

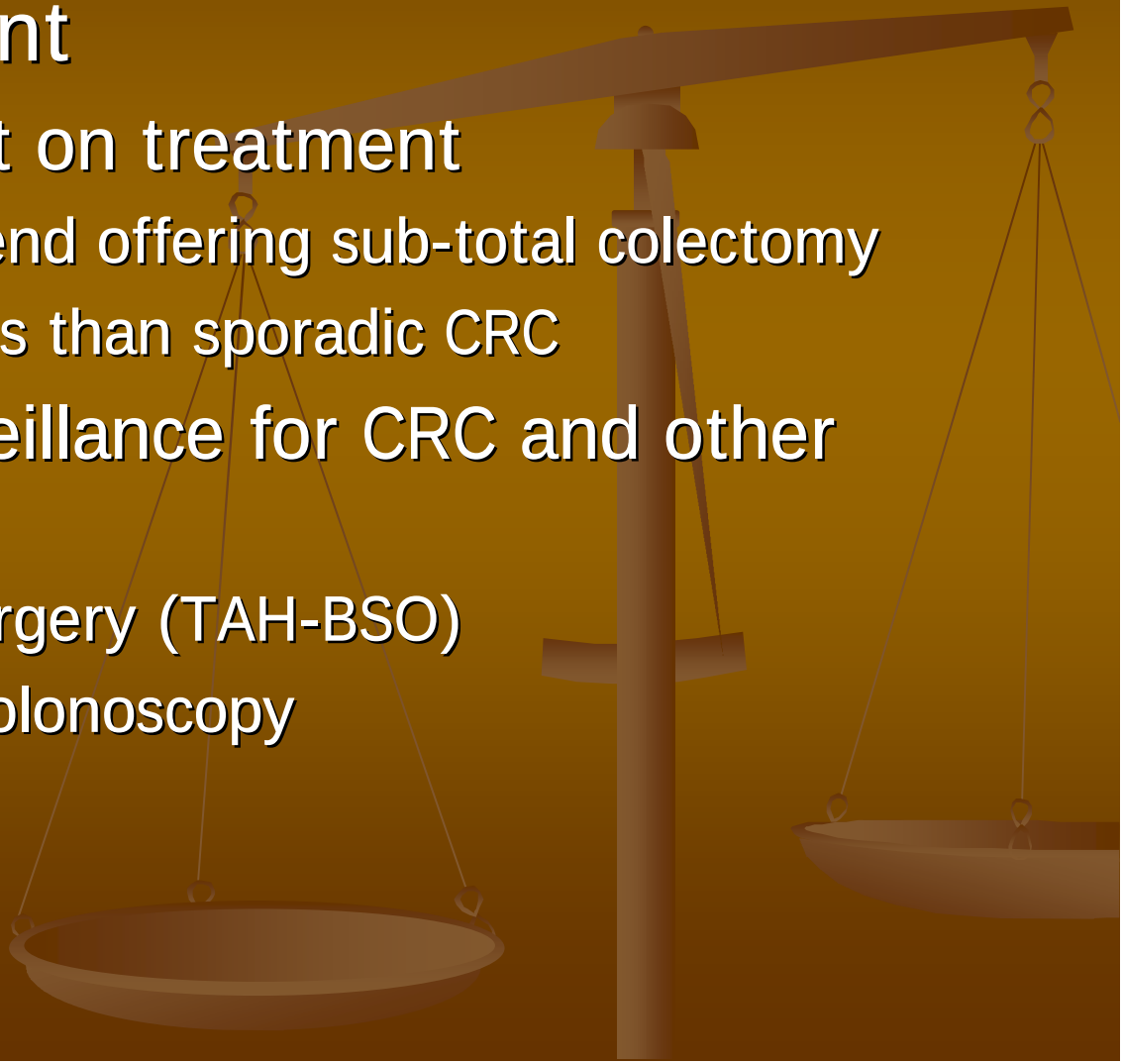


Lynch syndrome

- Also called Hereditary Non-Polyposis Colorectal Cancer syndrome (HNPCC)
  - 2-4% of all colon cancers
  - Associated with small numbers of polyps
  - Increased risk of cancers of the stomach, small intestine, liver, gallbladder ducts, upper urinary tract, brain, skin, and prostate
  - Women at increased risk for endometrial and ovarian cancer
  - Four DNA mismatch repair genes (MMR) responsible
    - Autosomal dominant inheritance
    - Mutation carriers have 20-65% lifetime risk of CRC

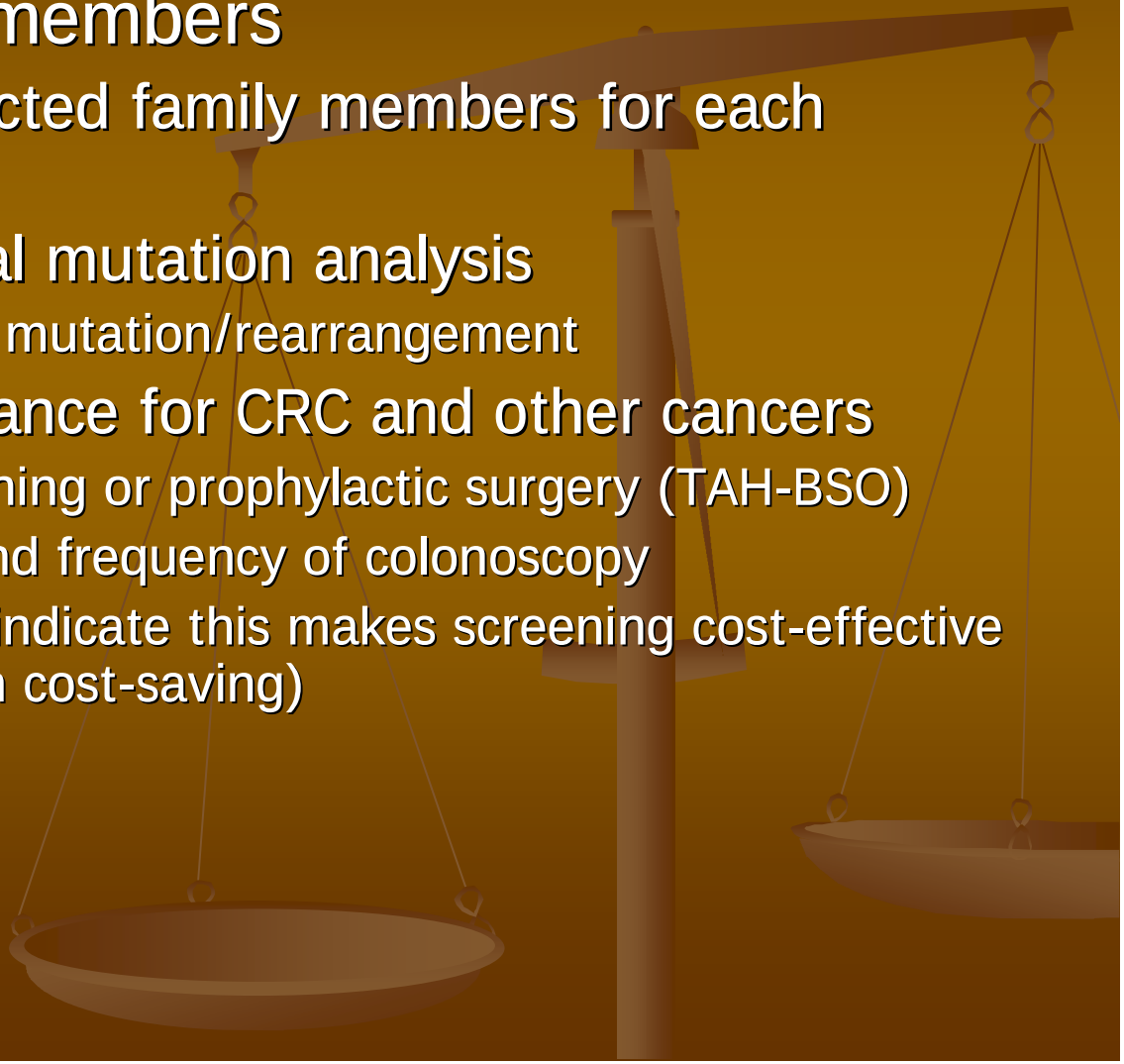
Lynch syndrome screening-Why?

- Impact on patient
  - Potential impact on treatment
    - Some recommend offering sub-total colectomy
    - Better prognosis than sporadic CRC
  - Impact on surveillance for CRC and other cancers
    - Prophylactic surgery (TAH-BSO)
    - Frequency of colonoscopy



Lynch syndrome screening-Why?

- Impact on family members
  - On average 3 affected family members for each proband
  - Low cost of familial mutation analysis
    - Looking for family mutation/rearrangement
  - Impact on surveillance for CRC and other cancers
    - Endometrial screening or prophylactic surgery (TAH-BSO)
    - Age of initiation and frequency of colonoscopy
    - Published models indicate this makes screening cost-effective (and perhaps even cost-saving)



Lynch syndrome-Public Health Impact

- 142,000 newly diagnosed cases of CRC annually
  - ~4250 have LS (based on 3% prevalence
  - ~8500-12750 relatives of probands with LS
- Highly effective screening test
  - Screening recommendations for LS patients different
    - Screen early
    - Decreased interval between screens
- Definitive diagnostic test
- Effective interventions if pre-cancerous polyps detected
  - Estimate prevent ~2500 cases of CRC annually

Lynch syndrome- Possible screening strategies

- Positive family history of CRC and associated cancers
  - Amsterdam and Bethesda criteria
- Tumor characteristics (Medullary growth, mucinous, signet ring, lymphocytic infiltration)
- Younger age of onset
- Presence of synchronous and/or metachronous CRC

All are insufficiently sensitive to identify more than 50% of patients alone or in combination

Lynch syndrome-new strategy

- Screen tumors of patients presenting with CRC using techniques specific to Lynch syndrome
  - If screen positive confirm with mutation testing
  - Followed by famililal case finding in confirmed +
- Two potential techniques
  - Assess tumor for micro-satellite instability
    - Pursue additional testing for patients whose tumor is unstable
  - Use immunohistochemical (IHC) staining of the MMR proteins
    - Pursue additional testing for patients with abnormal staining

Lynch syndrome screening- Evidence

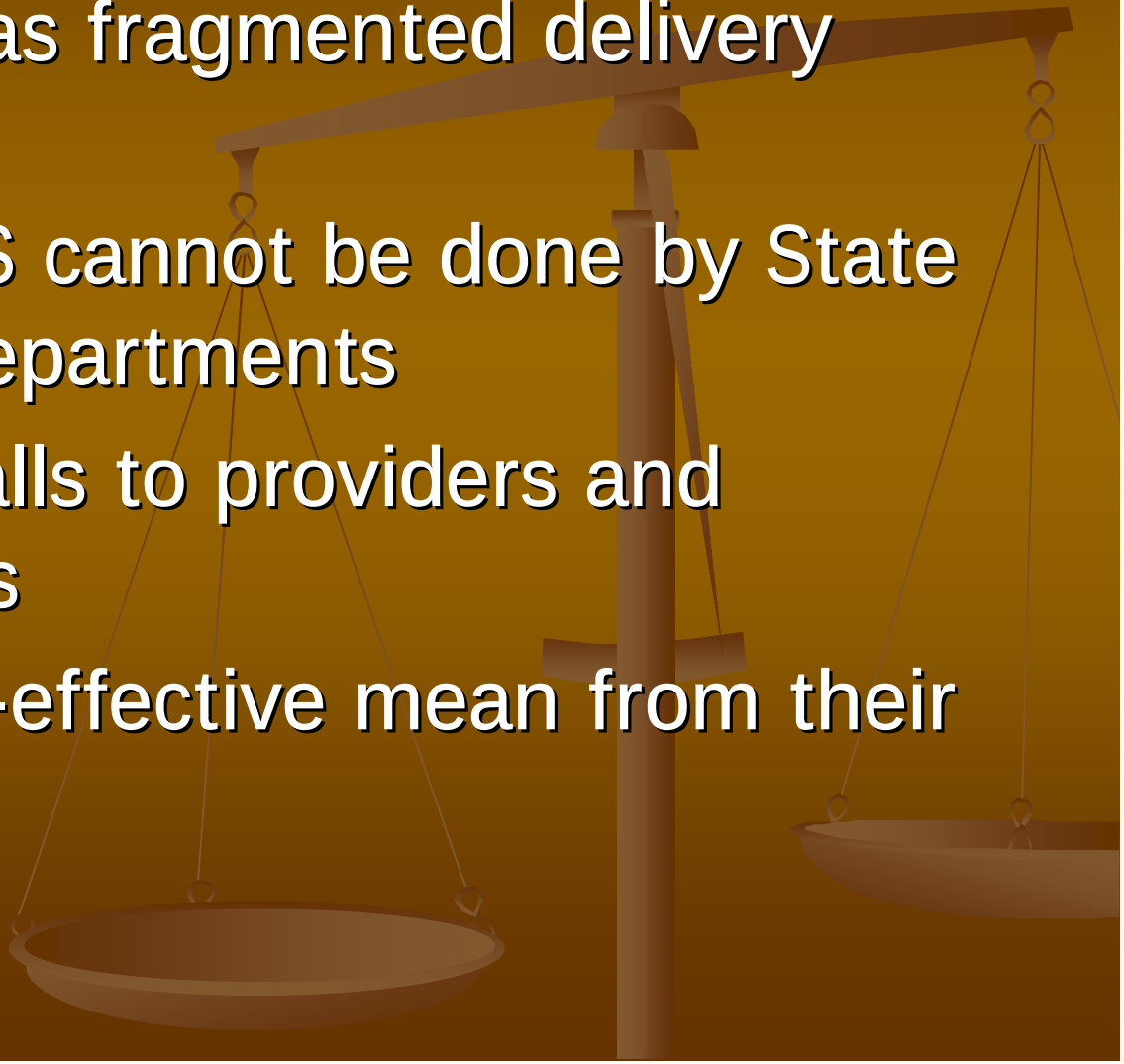
- Recommendations published January 2009 by Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group
- Confirms FH inconsistent screen compared to tumor-based testing
- Supports tumor based testing approach
  - Evidence insufficient to determine if IHC or MSI screening superior
    - Some evidence for role of *BRAF* testing if MLH1 stain abnormal
  - Adequate evidence of clinical utility *if* relatives identified, tested and comply with enhanced screening
- Little evidence on cost-benefit

Lynch syndrome screening- Evidence

- Cost-effectiveness (Mvundra et al. 2010)
  - Screening for LS in all newly diagnosed CRC ICER of </=$45,000/life year saved compared with no testing
    - If restrict testing to cases presenting under age 50 ICER increases to </=$75,000
  - Modeled IHC-first and MSI-first screening
    - IHC superior first screen with ICER </=$25,000/life year saved
  - Conclusion: tumor based screening cost effective from US health care system perspective

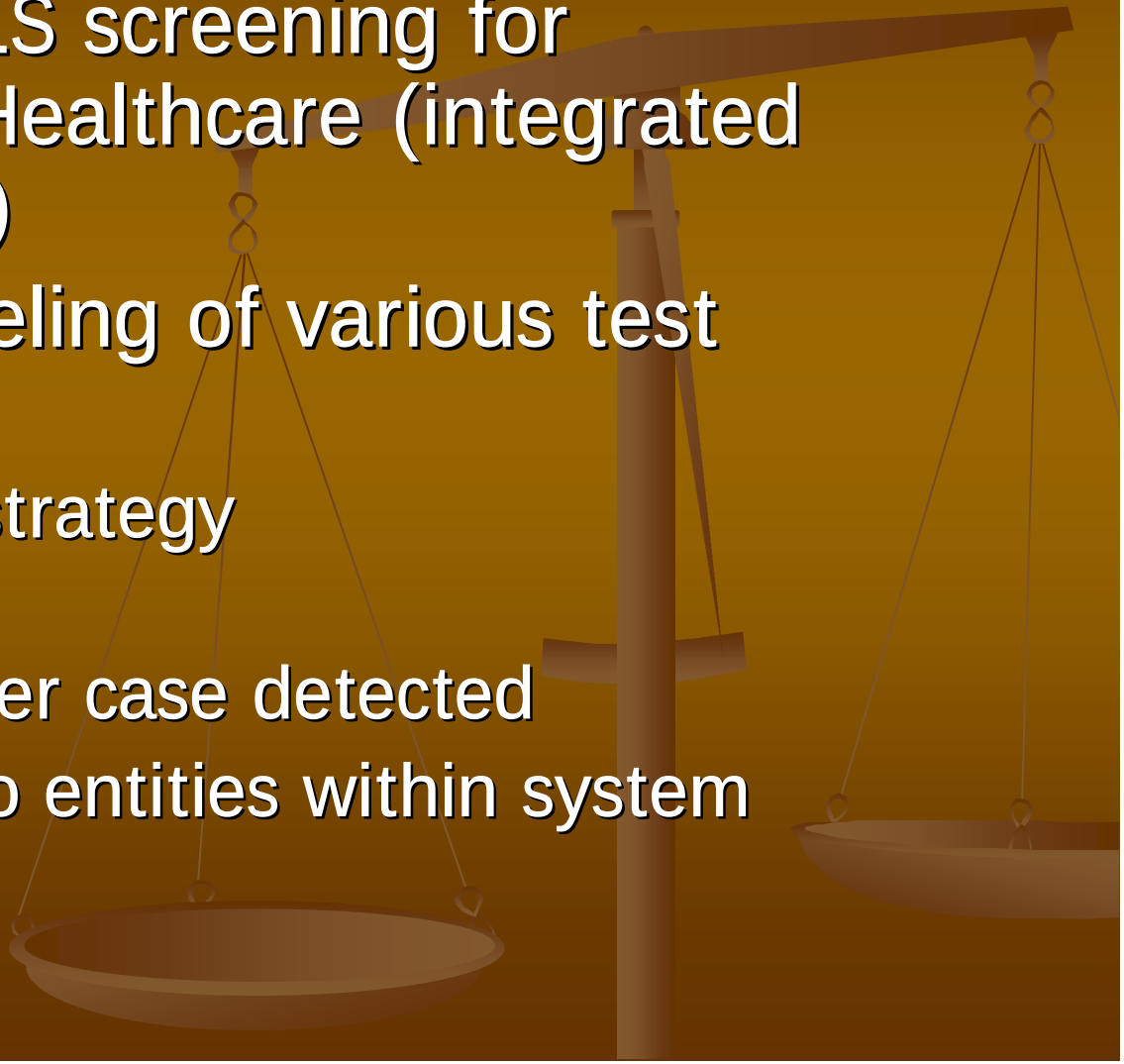
What is Public Health?

- United States has fragmented delivery system
- Screening for LS cannot be done by State Public Health Departments
- Responsibility falls to providers and delivery systems
- What does cost-effective mean from their perspective?



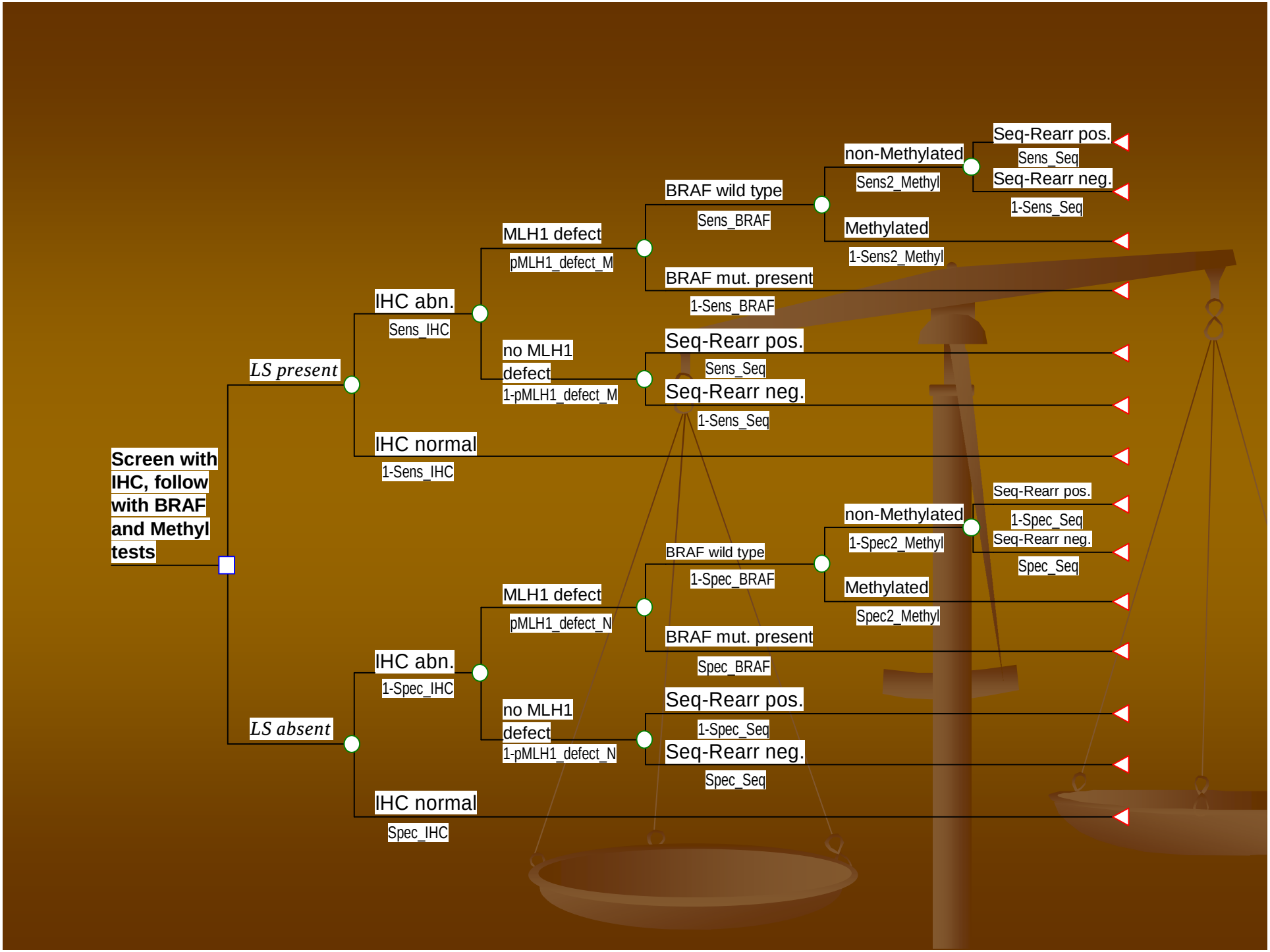
Illustration

- Assessment of LS screening for Intermountain Healthcare (integrated delivery system)
- Did formal modeling of various test scenarios
  - Used IHC-first strategy
    - No age cut-off
  - Endpoint cost per case detected
  - Assigned cost to entities within system



variable description	base	range	source	cost	distribution
IHC sensitivity	.94	.90—.98	Hampel, ++	$230*	triangular
IHC specificity	.88	.84—.92	Hampel, ++		triangular
BRAF sensitivity	.69	.57—.79	Palomaki	$305	triangular
BRAF specificity	.995	.98—1.0	Palomaki		triangular
Seq-Rearr sensitivity	.99	.98—1.0	++, others	$1,380*	triangular
Seq- Rearr specificity	.99	.98—1.0	++, others		triangular
Methyl. sensitivity	.93	.88—.98	Bouzourene, Chang	$295*	triangular
Methyl. specificity	.98	.95—1.0	Bouzourene, Chang		triangular
Methyl. sensi-2 (after *BRAF*)	.925	.875—.975	Bouzourene, Chang	$295*	triangular
Methyl. spec-2 (after *BRAF*)	.99	.95—1.0	Bouzourene, Chang		triangular
prevalence of LS among all CRC cases	0.036	.028—.044	Hampel, expert opinion	--	beta general
propor. of *MLH1* defects among abn. IHC given presence of LS	0.2353	.1985—.272	calculated from Hampel et al 2008 and 2005	--	beta general
propor. of *MLH1* defects among abn. IHC given absence of LS	0.8148	.733—.8985	calculated from Hampel et al 2008 and 2005	--	beta general

*True costs from referral lab used


Screen with IHC, follow with BRAF and Methyl tests
LS present
IHC abn.
Sens_IHC
MLH1 defect
pMLH1_defect_M
BRAF wild type
Sens_BRAF
non-Methylated
Sens2_Methyl
Seq-Rearr pos.
Sens_Seq
Seq-Rearr neg.
1-Sens_Seq
Methylated
1-Sens2_Methyl
BRAF mut. present
1-Sens_BRAF
no MLH1 defect
1-pMLH1_defect_M
Seq-Rearr pos.
Sens_Seq
Seq-Rearr neg.
1-Sens_Seq
IHC normal
1-Sens_IHC
LS absent
IHC abn.
1-Spec_IHC
MLH1 defect
pMLH1_defect_N
BRAF wild type
1-Spec_BRAF
non-Methylated
1-Spec2_Methyl
Seq-Rearr pos.
1-Spec_Seq
Seq-Rearr neg.
Spec_Seq
Methylated
Spec2_Methyl
BRAF mut. present
Spec_BRAF
no MLH1 defect
1-pMLH1_defect_N
Seq-Rearr pos.
1-Spec_Seq
Seq-Rearr neg.
Spec_Seq
IHC normal
Spec_IHC

100 CRC cases protocol	total cost to test	incremental increase in cost	# LS cases found	increase in cases found versus protocol above	average cost per case detected	cost to find additional case of LS
IHC with *BRAF* and Methylation	$35,203	--	3.28	--	**$10,730**	--
IHC with Methylation (no *BRAF*)	$37,369	$2,166	3.29	0.0076	**$11,363**	285,807
IHC with *BRAF* (no Methylation)	$38,338	$969	3.34	0.0512	**$11,481**	$19,056
IHC straight to Sequencing	$44,652	$6,313	3.35	0.0039	**$13,355**	$1,604,113

Outcomes

Measure	Report
# of CRC cases	Path auto-report
Breakdown by hospital	Path auto-report
# CRC cases sent for IHC	Path auto-report
# IHC normal	Path auto-report
# IHC abnormal	Path auto-report
# MSH2, MSH6, PMS2 abnormal	Path auto-report
# MLH1 abnormal *BRAF* +	Path auto-report
# MLH1 abnormal promoter methylation +	Path auto-report
# MLH1 abnormal, *BRAF* and methylation -	Path auto-report
# true positive patients contacted by CGC	Jim / Janet
# true positive patient physicians contacted by CGC	Jim / Janet
# attending counseling session	Jim / Janet
# declining counseling (reason)	Jim / Janet
# pursuing confirmatory genetic testing	Jim / Janet
# declining confirmatory genetic testing (reason)	Jim / Janet
# tested with mutation found	Jim / Janet
# tested with no mutation found	Jim / Janet
Insurance coverage for testing	Jim / Janet
For mutation + patients--Relatives	
# at risk relatives	Jim / Janet
# presenting for counseling	Jim / Janet
# pursuing familial mutation testing	Jim / Janet
# mutation +	Jim / Janet
# mutation -	Jim / Janet
# declining testing (reason)	
# relatives pursuing screening (type)	Jim / Janet
Mutation +	Jim / Janet
Mutation -	Jim / Janet
Mutation unknown	Jim / Janet
# patients with polyps	Jim / Janet
# patients with CRC	Jim / Janet
Stage	Jim / Janet

Lynch syndrome-Impact on delivery system

- Improved quality and consistency of care
- Hospital bears cost of screening program (DRG)
- Increased revenue for providers, hospitals, outpatient surgery centers
- Opportunity to bring new patients into system
- Small increase in costs for health plan
  - Potential for significant avoided costs due to prevention of cancer (particularly in relatives)
  - Consistent with coverage benefit?

Impact on patients and family

- Patient
  - Information on surveillance
  - Possible impact on treatment
  - Prognosis better
  - Privacy issues
    - Mitigated as they already have expressed disease
- Family
  - Identify high risk individuals
  - Opportunities for primary prevention in high risk individuals
  - Reassurance for family members without Lynch syndrome
    - Perhaps greater risk as disease may not be manifest in many

Reaction to information

- Intermountain Healthcare chose to implement
  - Information sheet provided
  - No consent for IHC
  - Full counseling and consent for confirmatory mutation testing (patient and family)
- Variations implemented at 24 other systems (e.g. Mayo, Cleveland Clinic, 20 use age cutoff, 4 screen all)

Reactor Panel

- Andrew Spiegel, CEO, Colon Cancer Alliance
- Mark Boguski, Associate Professor, Center for Biomedical Informatics, Harvard Medical School
- Roy Gandolfi, Associate Medical Director, SelectHealth
- Dennis Salisbury, Family Practice Physician, Rocky Mountain Clinic, Butte, MT
- Don Lyman, Chief, Chronic Disease and Injury Control Division, California Department of Public Health