Evidence Assessment for Returning Results from Genome Sequencing

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Acknowledgments

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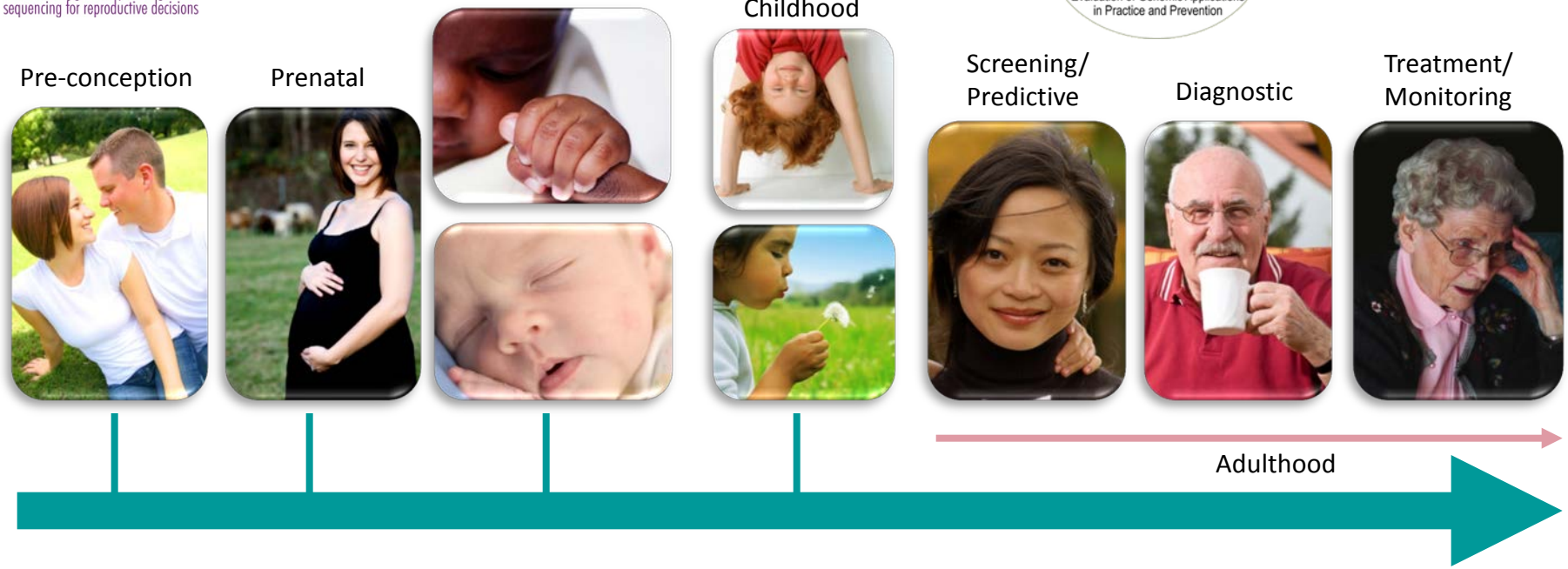
Goddard, Whitlock, Berg, Williams, Webber, Webster, Lin, Schrader, Campos-Outcalt, Offit, Feigelson, Hollombe, **Description and pilot results from a novel method for evaluating return of incidental findings from next generation sequencing technologies**. *Genet Med* 2013 15(9): 721-8.

Clinical Context

NextGen
Understanding the impact of genome sequencing for reproductive decisions

Evidence to Practice
EGAPP
Evaluation of Genomic Applications in Practice and Prevention

ClinGen



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How do we select genes/conditions for full evidence review and evaluation?

- Topics are initially proposed through processes that typically rely on subject matter experts and/or based on priorities of funding agencies
- Topics are selected for full review and evaluation based on availability of evidence and minimal thresholds (stage I)

How do we define Actionability?

Adult Incidental Findings

ACTIONABILITY

1. Is there a practice guideline or systematic review for the genetic condition?

2. Does the practice guideline or systematic review indicate that the result is actionable in *one or more* of the following ways?

- Patient Management
- Surveillance or Screening
- Family Management
- Circumstances to Avoid

3. Is the result actionable in an undiagnosed adult with the genetic condition?

NOT ACTIONABILITY

Topic	Rational for exclusion
End of diagnostic odyssey	IFs are not related to the indication for testing
Reproductive decision making	Not relevant for all patients in our clinical scenario
Personal utility: value of knowing the information	Not actionable in a clinical context

Actionability for Preconception Carrier Status Screening

NextGen
Understanding the impact of genome sequencing for reproductive decisions

Categories	Description
Shortened Lifespan	Most children do not live past early childhood, even with medical interventions
Serious	Most children will have medical problems that require regular medical visits, daily medications, carefully monitored diets, or surgeries; or will have serious problems with learning, vision, hearing or mobility. Children may have shortened life spans into early adulthood.
Mild/ Moderate	Most children will have medical problems that require occasional extra medical visits, occasional medications, a slightly modified diet, or surgery; or will have mild problems with learning, vision, hearing, or mobility.
Unpredictable	It is difficult to predict the outcome for many children with these conditions. Some children will have more serious versions but others will have more mild versions or no problems at all.
Adult Onset	Few have any symptoms as children, but medical, behavioral, vision, or hearing problems may begin as adults.

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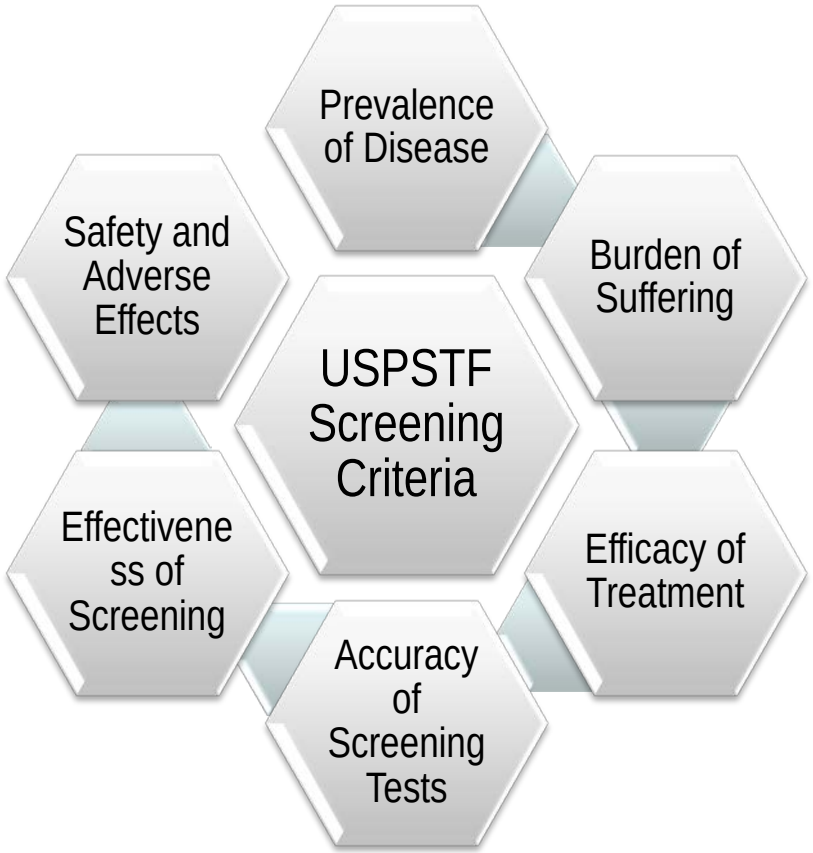
Population Screening Framework

- Wilson & Jungner, WHO Criteria, 1968
- Screening in newborns & children
  - Calonge et al., Genet Med 2010
  - Watson et al., Ment Retard Dev Disabil Res Rev 2006
- UK National Screening Committee Criteria, 2012
- Population screening programs in genomic medicine
  - Khoury et al., N Engl J Med, 2003
  - Burke et al., Epidemiol Rev, 2011
- Harris et al., Evaluating proposed screening programs, USPSTF, Epidemiol Rev, 2011



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“Binning” Framework

	Criteria:	*Clinical Utility*	*Clinical Validity*			*Unknown Clinical Implications*
Genes	Bins:	**Bin 1 Medically actionable incidental information**	**Bin 2A Low risk incidental information**	**Bin 2B Medium risk incidental information**	**Bin 2C High risk incidental information**	**Bin 3**
	Examples:	*BRCA1/2 MLH1, MSH2 FBN1 NF1*	PGx variants and common risk SNPs	*APOE* Carrier status for recessive Mendelian disorders	Huntington Prion diseases ALS (SOD1)	**All other loci**
	Estimated number of genes/loci:	10s	10s (eventually 100s – 1000s)	1000s	10s	~20,000

Berg, Khoury, Evans, Genet Med, 2011

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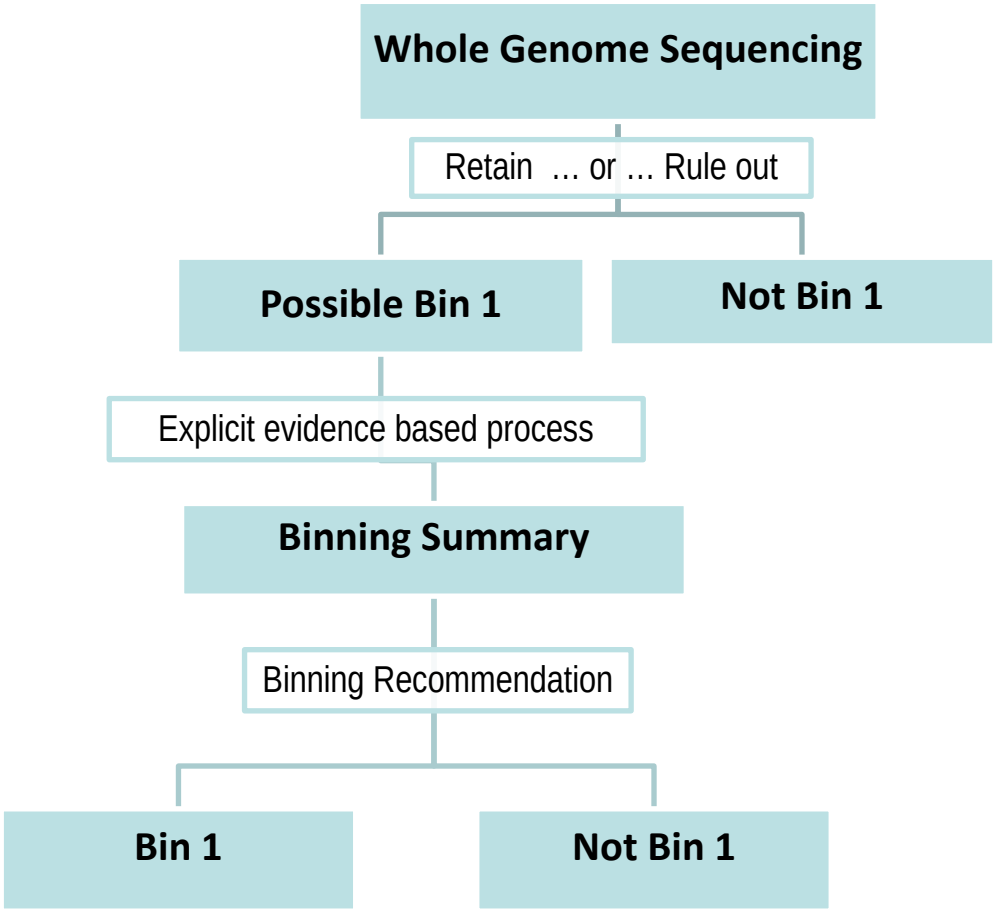
Process Overview



Stage 1

Stage 2

Evidence to Practice
EGAPP
Evaluation of Genomic Applications in Practice and Prevention

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Stage 1: Early Rule-Out Criteria

ACTIONABILITY

1. Is there a practice guideline or systematic review for the genetic condition?

2. Does the practice guideline or systematic review indicate that the result is actionable in *one or more* of the following ways?

- Patient Management
- Surveillance or Screening
- Family Management
- Circumstances to Avoid

3. Is the result actionable in an undiagnosed adult with the genetic condition?

PENETRANCE

4. Is there at least one known pathogenic variant with at least moderate penetrance (>40%) or moderate relative risk (>2.0) in any population?

SIGNIFICANCE

5. Is this condition an important health problem?

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Stage 2: Criteria

Stage 1	Stage 2
Actionability	How effective are interventions for preventing the harm?
Penetrance	What is the chance that this threat will materialize?
Significance	What is the nature of the threat to health for an individual carrying a deleterious allele?
	How acceptable are the interventions in terms of the burdens or risks placed on the individual?
	Would the underlying risk or condition escape detection prior to harm in the setting of recommended care?

What process do we use to identify studies and data?

- We use explicit and reproducible search methods
- Methods limited and feasible
  - We restrict the type of data sources to systematic reviews, evidence based practice guidelines, or expert consensus based practice guidelines with or without reference to primary literature
- Not comprehensive

Step	Method
1	Identify synonyms for the condition, name of involved gene(s), and the OMIM identification number from OMIM and Gene Test Reviews
2	If a GeneTest Review exists, search for a link to a treatment guideline within the text or reference list.
3	Search OMIM for a link to a guideline.
4	Search guidelines.gov for condition name and any synonyms identified in step 1.
5	Search PubMed for “practice guidelines” and “systematic reviews” using MeSH terms.
6	If no relevant MeSH term is identified or the term is too broad, search PubMed using the condition or gene name as text words.
7	Search for summaries under OrphaNet or Clinical Utility Gene Cards.

How do we critically assess the data and synthesize for conclusion?

- Tiers of evidence
  - To gain efficiency in reviewing evidence
  - To address expected volume and disagreement among sources
  - To signal overall quality of sources
- Quality Rating
  - As a 'tie breaker' for conflicting evidence at the same tier
  - Method
    - Tier 1: AMSTAR
    - Tier 2: AGREE II Criteria

Tiers of Evidence

Step 3: Determine Tier of Evidence for each Source.

First tier

- Evidence from a systematic review, or a meta-analysis, or a clinical practice guideline clearly based on a systematic review[1]

Second tier

- Evidence from clinical practice guidelines or broad-based expert consensus with some level of evidence review, but using unclear methods or using sources that were not systematically identified[1]

Third tier

- Evidence from another source with non-systematic review of evidence (e.g., GeneTest Reviews, OrphaNet, and Clinical Utility Gene Cards, opinion of a single or few (<5) experts) with additional primary literature cited

Fourth tier

- Evidence from another source with non-systematic review of evidence (e.g., GeneTest Reviews, OrphaNet, and Clinical Utility Gene Cards, opinion of a single or few (<5) experts) with no citations to primary data sources

[1]systematic review of evidence means that traditional systematic review methods are followed including: a) a clearly stated set of objectives, b) an explicit, reproducible methodology, c) systematic search that attempts to identify all studies that would meet the eligibility criteria, d) inclusion and exclusion criteria for studies are pre-defined, and e) an assessment of the validity of findings in the included studies, and f) a systematic presentation and synthesis of the characteristics and findings of the included studies. (http://www.cochrane-handbook.org/)

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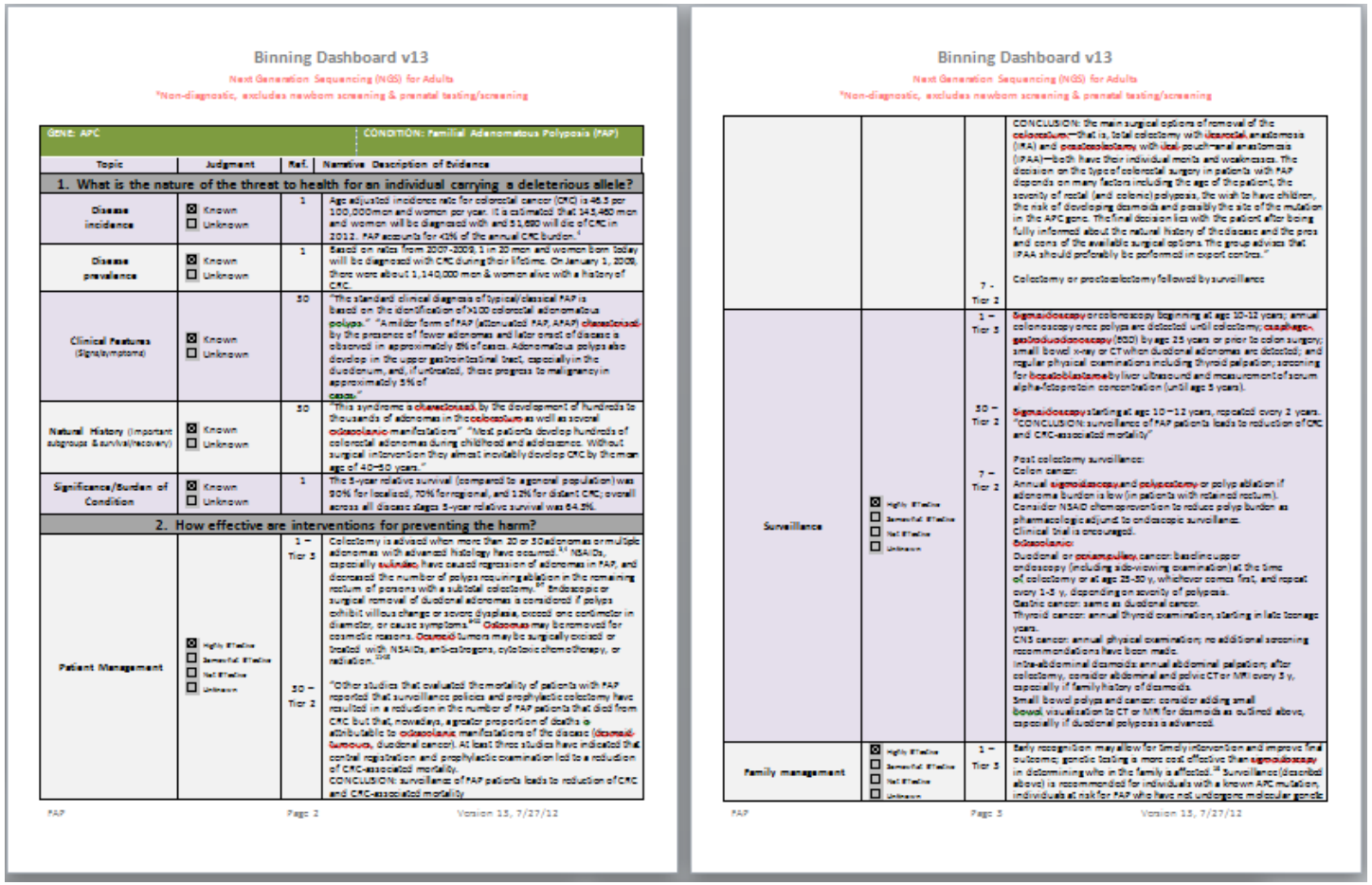
How do we present the results to policy makers?



Binning Dashboard v13

Next Generation Sequencing (NGS) for Adults

*Non-diagnostic, excludes newborn screening & prenatal testing/screening

GENE: APC			CONDITION: Familial Adenomatous Polyposis (FAP)
Topic	**Judgment**	**Ref.**	**Narrative Description of Evidence**
1. What is the nature of the threat to health for an individual carrying a deleterious allele?			
Disease incidence	☒ Known ☐ Unknown	1	Age adjusted incidence rate for colorectal cancer (CRC) is 46.3 per 100,000 men and women per year. It is estimated that 143,460 men and women will be diagnosed with and 51,690 will die of CRC in 2012. FAP accounts for <1% of the annual CRC burden.[1]
Disease prevalence	☒ Known ☐ Unknown	1	Based on rates from 2007-2009, 1 in 20 men and women born today will be diagnosed with CRC during their lifetime. On January 1, 2009, there were about 1,140,000 men & women alive with a history of CRC.
Clinical Features (Signs/symptoms)	☒ Known ☐ Unknown	50	"The standard clinical diagnosis of typical/classical FAP is based on the identification of >100 colorectal adenomatous polyps." "A milder form of FAP (attenuated FAP, AFAP) characterized by the presence of fewer adenomas and later onset of disease is observed in approximately 8% of cases. Adenomatous polyps also develop in the upper gastrointestinal tract, especially in the duodenum, and, if untreated, these progress to malignancy in approximately 5% of cases."
Natural History (Important subgroups & survival/recovery)	☒ Known ☐ Unknown	50	"This syndrome is characterized by the development of hundreds to thousands of adenomas in the colon/rectum as well as several extracolonic manifestations" "Most patients develop hundreds of colorectal adenomas during childhood and adolescence. Without surgical intervention they almost inevitably develop CRC by the mean age of 40–50 years."
Significance/Burden of Condition	☒ Known ☐ Unknown	1	"The 5-year relative survival (compared to a general population) was 90% for localized, 70% for regional, and 12% for distant CRC; overall across all disease stages 5-year relative survival was 64.5%.
2. How effective are interventions for preventing the harm?			
Patient Management	☒ Highly Effective ☐ Somewhat Effective ☐ Not Effective ☐ Unknown	1 – Tier 3 50 – Tier 2	Colectomy is advised when more than 20 or 30 adenomas or multiple adenomas with advanced histology have occurred.[2,3] NSAIDs, especially sulindac, have caused regression of adenomas in FAP, and decreased the number of polyps requiring ablation in the remaining rectum of persons with a subtotal colectomy.[4] Endoscopic or surgical removal of duodenal adenomas is considered if polyps exhibit villous change or severe dysplasia, exceed one centimeter in diameter, or cause symptoms.[5,6] Osteomas may be removed for cosmetic reasons. Desmoid tumors may be surgically excised or treated with NSAIDs, anti-estrogens, cytotoxic chemotherapy, or radiation.[7,8] "Other studies that evaluated the mortality of patients with FAP reported that surveillance policies and prophylactic colectomy have resulted in a reduction in the number of FAP patients that died from CRC but that, nowadays, a greater proportion of deaths is attributable to extracolonic manifestations of the disease (desmoid tumours, duodenal cancer). At least three studies have indicated that central registration and prophylactic examination led to a reduction of CRC-associated mortality. CONCLUSION: surveillance of FAP patients leads to reduction of CRC and CRC-associated mortality

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Binning Dashboard v13

Next Generation Sequencing (NGS) for Adults

*Non-diagnostic, excludes newborn screening & prenatal testing/screening

		7 – Tier 2	CONCLUSION: The main surgical options of removal of the colorectum—that is, total colectomy with ileorectal anastomosis (IRA) and proctocolectomy with ileal-pouch–anal anastomosis (IPAA)—both have their individual merits and weaknesses. The decision on the type of colorectal surgery in patients with FAP depends on many factors including the age of the patient, the severity of rectal (and colonic) polyposis, the wish to have children, the risk of developing desmoids and possibly the site of the mutation in the APC gene. The final decision lies with the patient after being fully informed about the natural history of the disease and the pros and cons of the available surgical options. The group advises that IPAA should preferably be performed in expert centres." Colectomy or proctocolectomy followed by surveillance
Surveillance	☒ Highly Effective ☐ Somewhat Effective ☐ Not Effective ☐ Unknown	1 – Tier 3 50 – Tier 2 7 – Tier 2	Sigmoidoscopy or colonoscopy beginning at age 10-12 years; annual colonoscopy once polyps are detected until colectomy; esophago-gastroduodenoscopy (EGD) by age 25 years or prior to colon surgery; small bowel x-ray or CT when duodenal adenomas are detected; and regular physical examinations including thyroid palpation; screening for hepatoblastoma by liver ultrasound and measurement of serum alpha-fetoprotein concentration (until age 5 years). Sigmoidoscopy starting at age 10–12 years, repeated every 2 years. "CONCLUSION: surveillance of FAP patients leads to reduction of CRC and CRC-associated mortality" Post colectomy surveillance: Colon cancer: Annual sigmoidoscopy and polypectomy or polyp ablation if adenoma burden is low (in patients with retained rectum). Consider NSAID chemoprevention to reduce polyp burden as pharmacologic adjunct to endoscopic surveillance. Clinical trial is encouraged. Extracolonic: Duodenal or periampullary cancer: baseline upper endoscopy (including side-viewing examination) at the time of colectomy or at age 25-30 y, whichever comes first, and repeat every 1-3 y, depending on severity of polyposis. Gastric cancer: same as duodenal cancer. Thyroid cancer: annual thyroid examination, starting in late teenage years. CNS cancer: annual physical examination; no additional screening recommendations have been made. Intra-abdominal desmoids: annual abdominal palpation; after colectomy, consider abdominal and pelvic CT or MRI every 3 y, especially if family history of desmoids. Small bowel polyps and cancer: consider adding small bowel visualization to CT or MRI for desmoids as outlined above, especially if duodenal polyposis is advanced.
Family management	☒ Highly Effective ☐ Somewhat Effective ☐ Not Effective ☐ Unknown	1 – Tier 3	Early recognition may allow for timely intervention and improve final outcome; genetic testing is more cost effective than sigmoidoscopy in determining who in the family is affected.[9] Surveillance (described above) is recommended for individuals with a known APC mutation, individuals at risk for FAP who have not undergone molecular genetic

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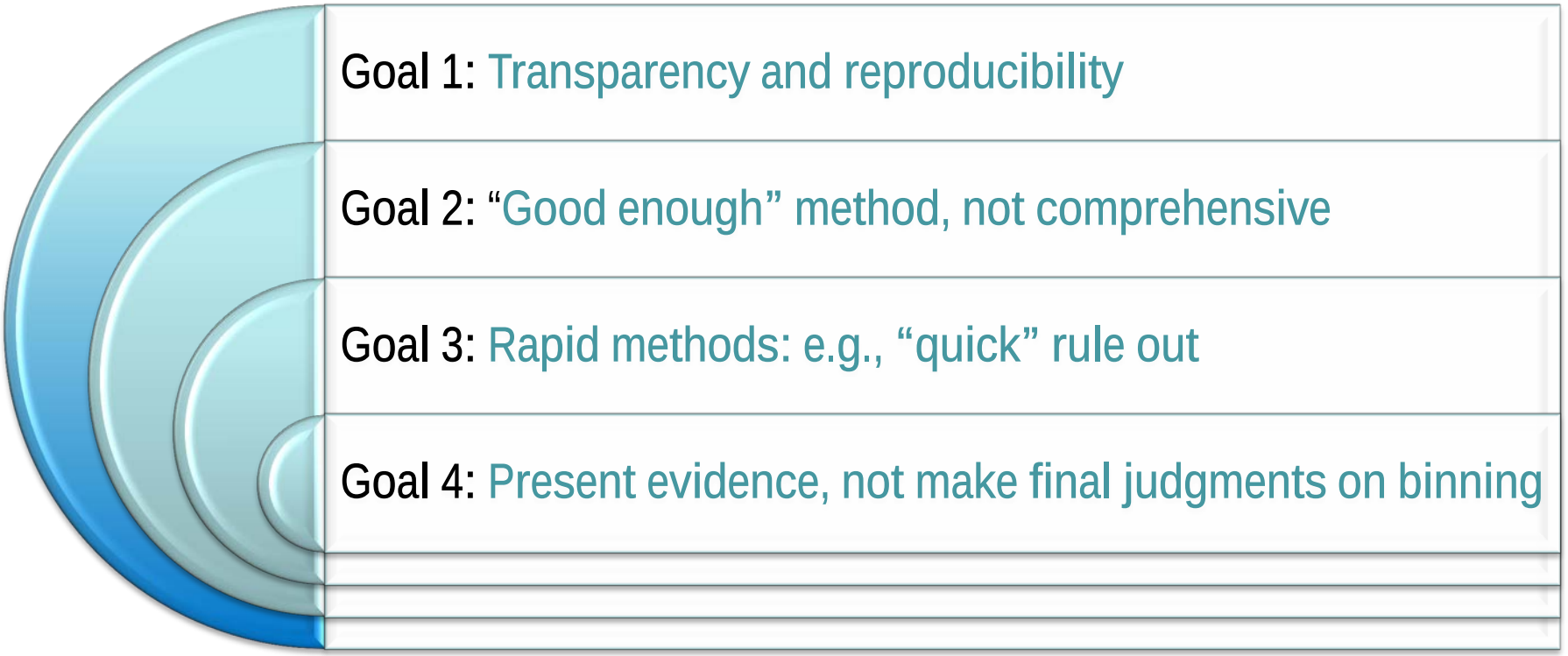
Summary



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Future Challenges

- Brevity vs. Comprehensiveness
- Conditions vs. Genes vs. Variant level
- Extrapolation from high risk populations to the general population
- Accounting for variation among individuals
  - X-linked conditions more highly relevant for males
  - Conditions with variable penetrance, e.g., carriers of BRCA mutations have different risks depending on the strength of family history
- Other clinical scenarios
  - Diagnostic setting
  - Newborn screening
  - Somatic mutations
- Methods for updating