Consent forms in genomics: assessing the privacy risks of data sharing

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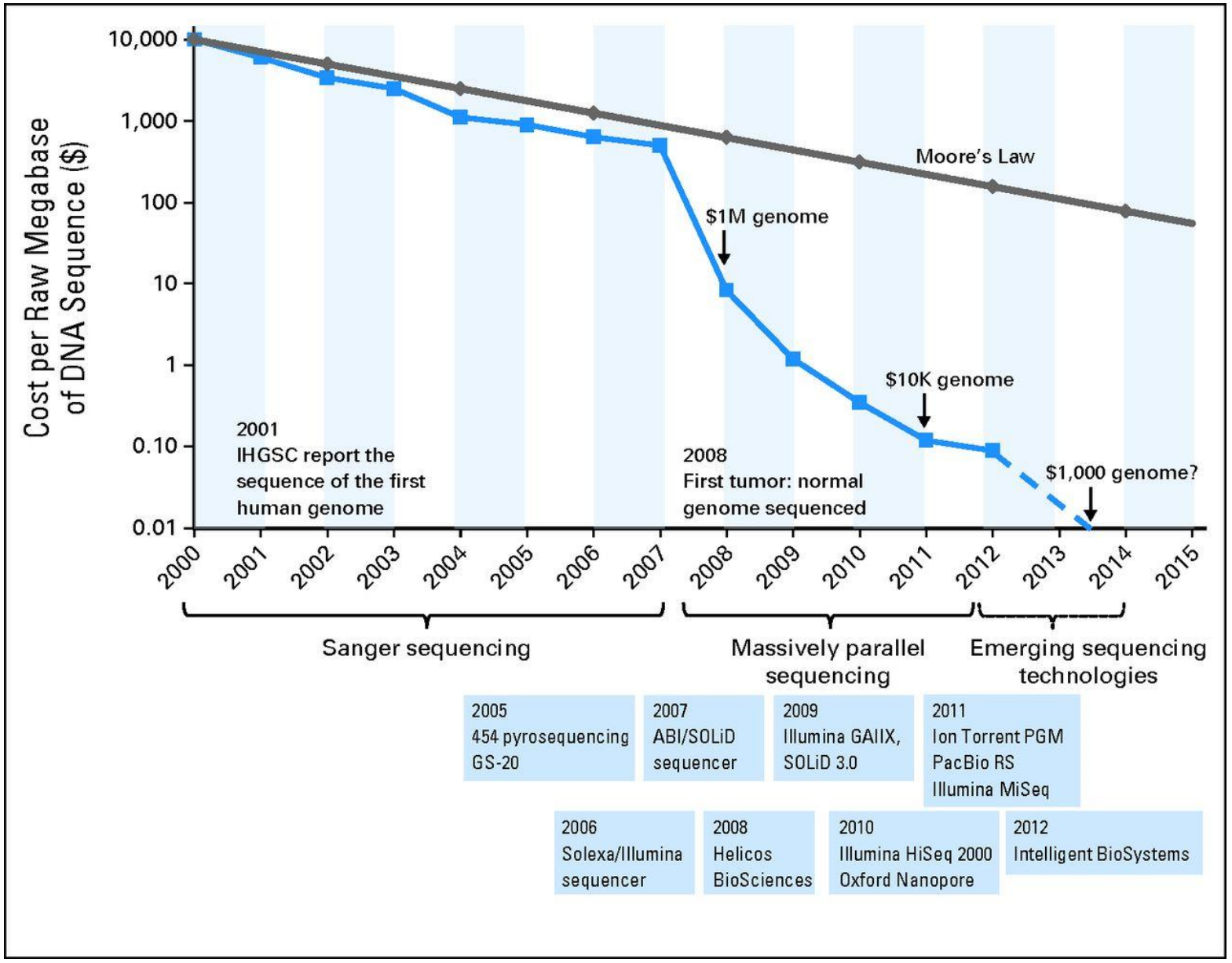


MacConaill, J Clin Onc 2013

New cancer treatment paradigm

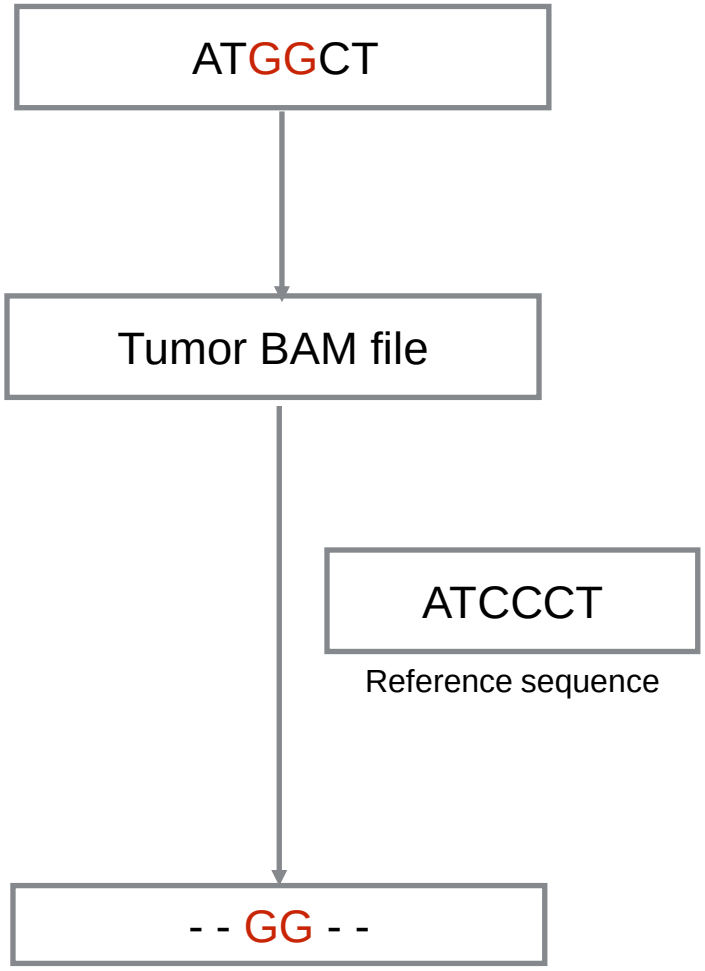
Consenting patients

- Clinical sequencing of tumors
- Consent and data privacy issues are related to **germline** sequence data, not tumor sequence
- Multiple approaches to somatic sequencing, which are non-equivalent in their use of germline data
  - Each of these requires a different approach to consenting
  - However, an individual physician decision about consenting tends to depend upon time, support and concerns about legal liability

Sources of germ line findings in tumor mutation profiling

- Indirect: germ line DNA sequence reflected in DNA of tumor
- Direct: germ line DNA sequence determined for comparison to tumor sequence

Tumor sequencing **without** matched normal



Could be <u>either</u> germ line <u>or</u> somatic

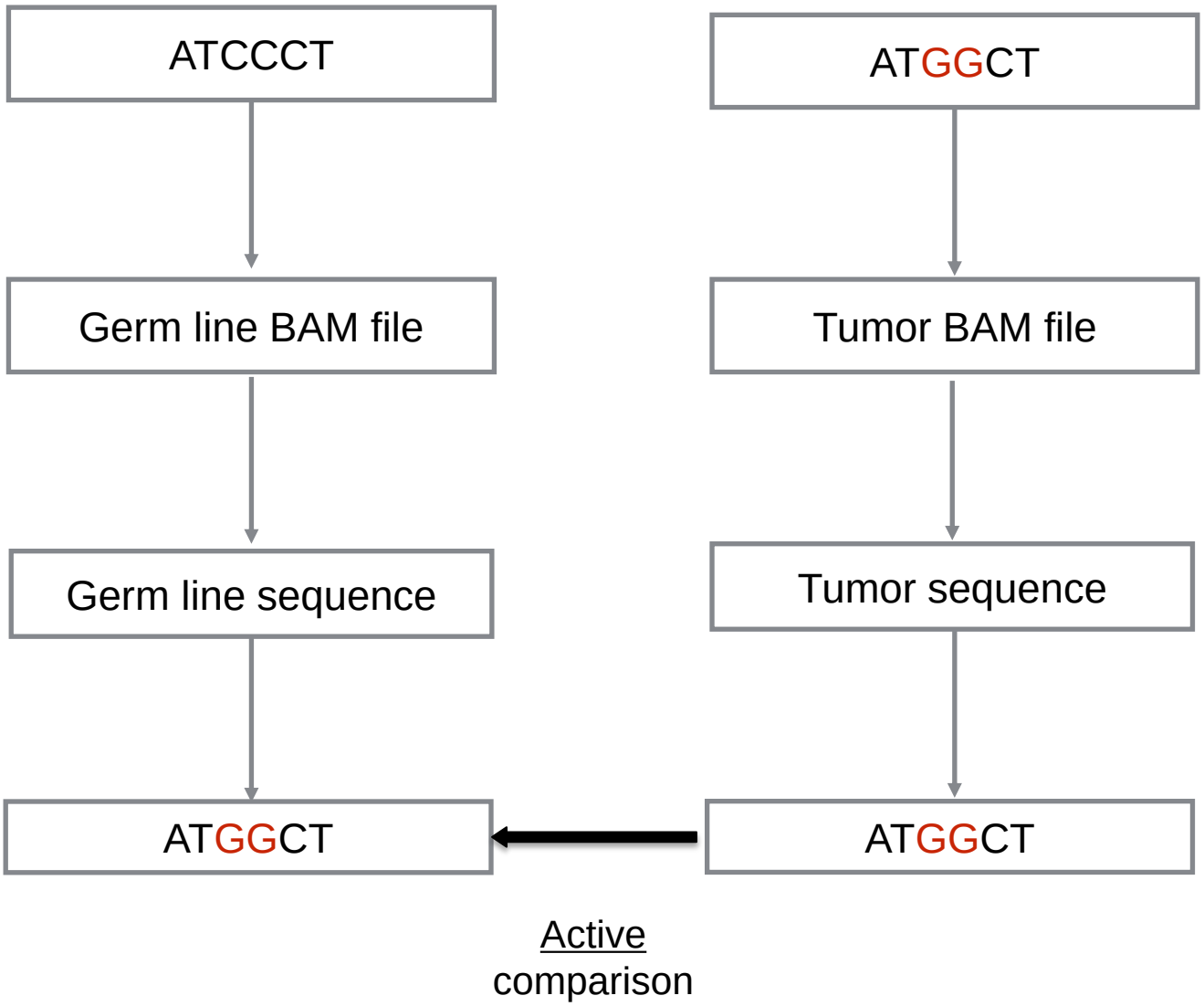
Current List of Foundation One Genes

ABL1	BTK	CTNNB1	FGF23	IL7R	MLH1	PDGFRA	SMO
AKT1	CARD11	DAXX	FGF3	INHBA	MLL	PDGFRB	SOCS1
AKT2	CBFB	DDR2	FGF4	IRF4	MLL2	PDK1	SOX10
AKT3	CBL	DNMT3A	FGF6	IRS2	MPL	PIK3CA	SOX2
ALK	CCND1	DOT1L	FGFR1	JAK1	MRE11A	PIK3CG	SPEN
APC	CCND2	EGFR	FGFR2	JAK2	MSH2	PIK3R1	SPOP
AR	CCND3	EMSY	FGFR3	JAK3	MSH6	PIK3R2	SRC
ARAF	CCNE1	EP300	FGFR4	JUN	MTOR	PPP2R1A	STAG2
ARFRP1	CD79A	EPHA3	FLT1	KAT6A	MUTYH	PRDM1	STAT4
ARID1A	CD79B	EPHA5	FLT3	KDM5A	MYC	PRKAR1A	STK11
ARID2	CDC73	EPHB1	FLT4	KDM5C	MYCL1	PRKDC	SUFU
ASXL1	CDH1	ERBB2	FOXL2	KDM6A	MYCN	PTCH1	TET2
ATM	CDK12	ERBB3	GATA1	KDR	MYD88	PTEN	TGFBR2
ATR	CDK4	ERBB4	GATA2	KEAP1	NF1	PTPN11	TNFAIP3
ATRX	CDK6	ERG	GATA3	KIT	NF2	RAD50	TNFRSF14
AURKA	CDK8	ESR1	GID4	KLHL6	NFE2L2	RAD51	TOP1
AURKB	CDKN1B	EZH2	GNA11	KRAS	NFKBIA	RAF1	TP53
AXL	CDKN2A	FAM123B	GNA13	LRP1B	NKX2-1	RARA	TSC1
BAP1	CDKN2B	FAM46C	GNAQ	MAP2K1	NOTCH1	RB1	TSC2
BARD1	CDKN2C	FANCA	GNAS	MAP2K2	NOTCH2	RET	TSHR
BCL2	CEBPA	FANCC	GPR124	MAP2K4	NPM1	RICTOR	VHL
BCL2L2	CHEK1	FANCD2	GRIN2A	MAP3K1	NRAS	RNF43	WISP3
BCL6	CHEK2	FANCE	GSK3B	MCL1	NTRK1	RPTOR	WT1
BCOR	CIC	FANCF	HGF	MDM2	NTRK2	RUNX1	XPO1
BCORL1	CREBBP	FANCG	HRAS	MDM4	NTRK3	SETD2	ZNF217
BLM	CRKL	FANCL	IDH1	MED12	NUP93	SF3B1	ZNF703
BRAF	CRLF2	FBXW7	IDH2	MEF2B	PAK3	SMAD2	
BRCA1	CSF1R	FGF10	IGF1R	MEN1	PALB2	SMAD4	
BRCA2	CTCF	FGF14	IKBKE	MET	PAX5	SMARCA4	
BRIP1	CTNNA1	FGF19	IKZF1	MITF	PBRM1	SMARCB1	

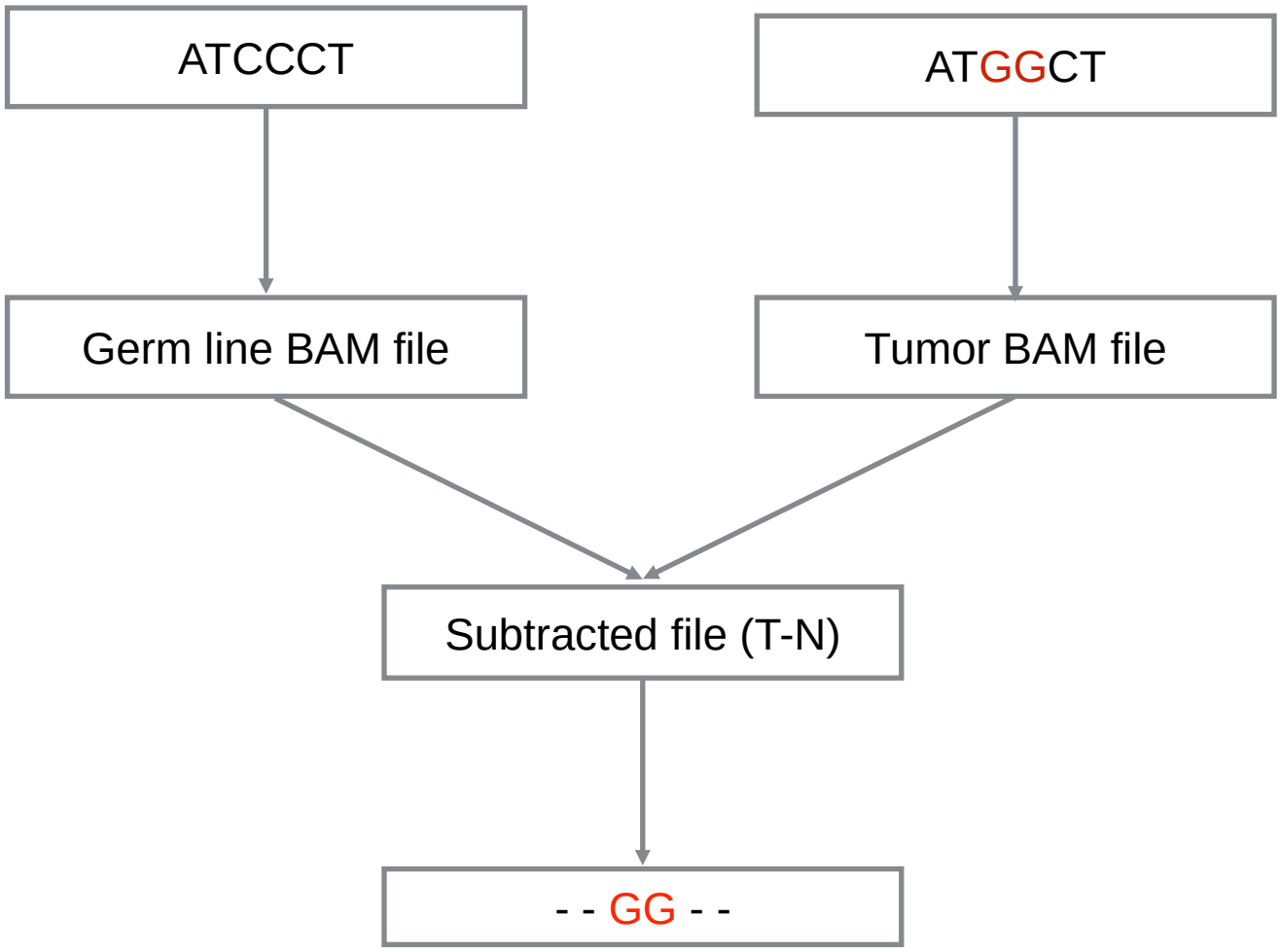
Which somatic variants to evaluate?

- Gene mutation consistent with phenotype
  - Important to go back to family history
- Known founder mutations
  - Ashkenazi Jewish *BRCA1/2* mutations
- Biallelic mutations in the tumor
- Functionally significant
  - Not variants of uncertain significance
- Allelic ratio in tumor

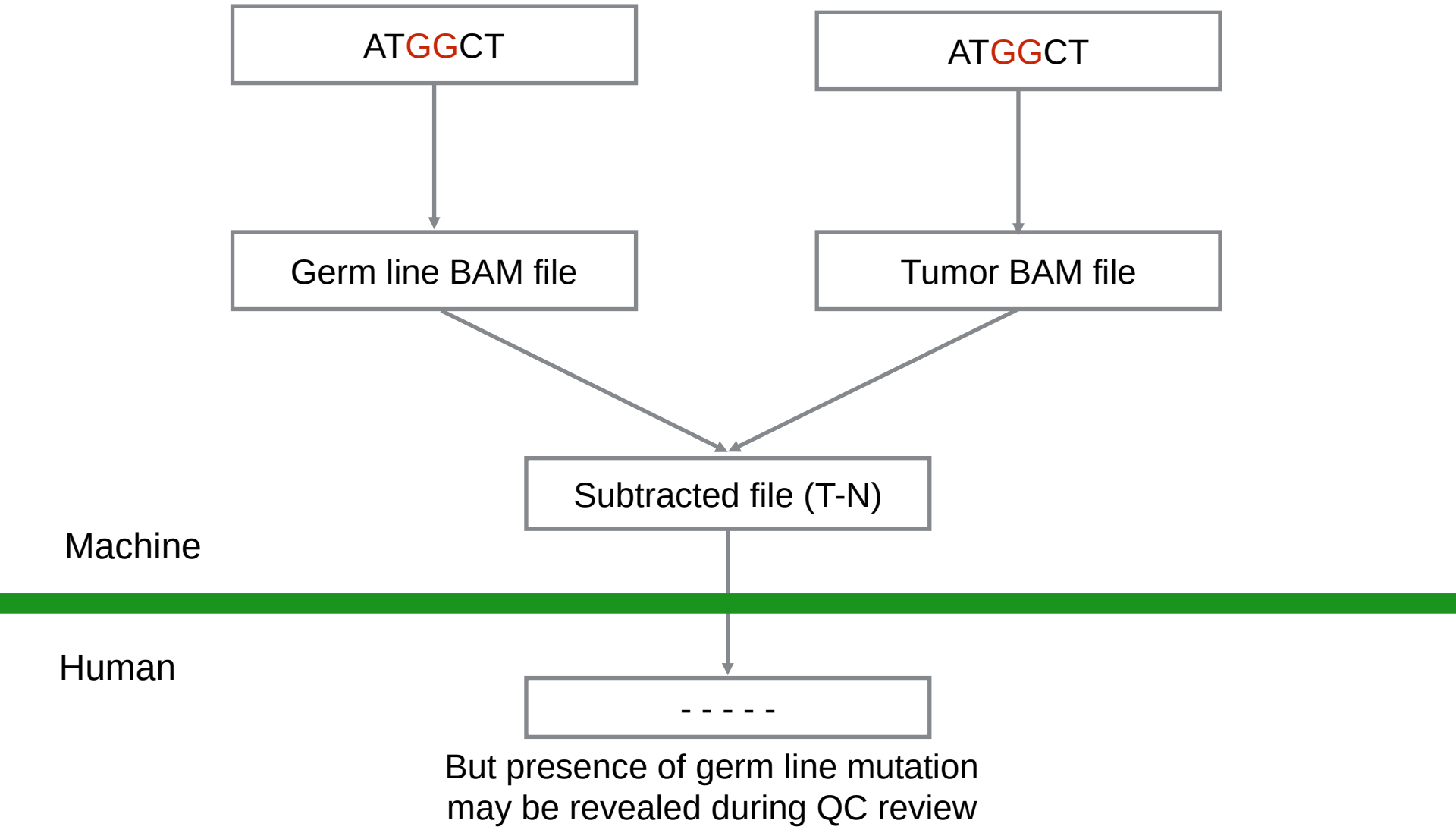
Tumor sequencing **with** germline normal



Subtracting out the germline

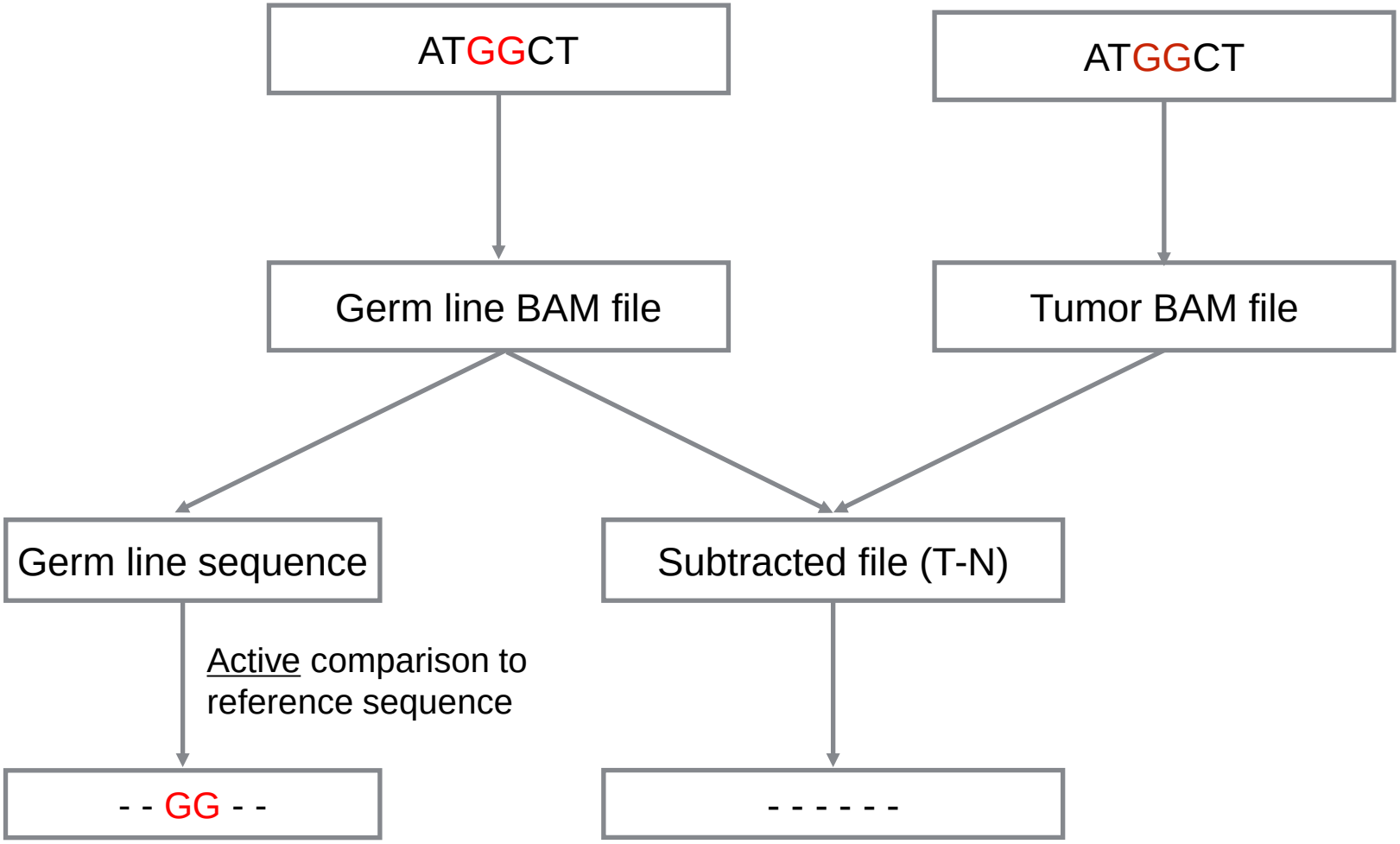


Germ line variants are actively **obscured** by subtraction algorithms



But presence of germ line mutation
may be revealed during QC review

Direct generation of germ line findings when profiling tumors



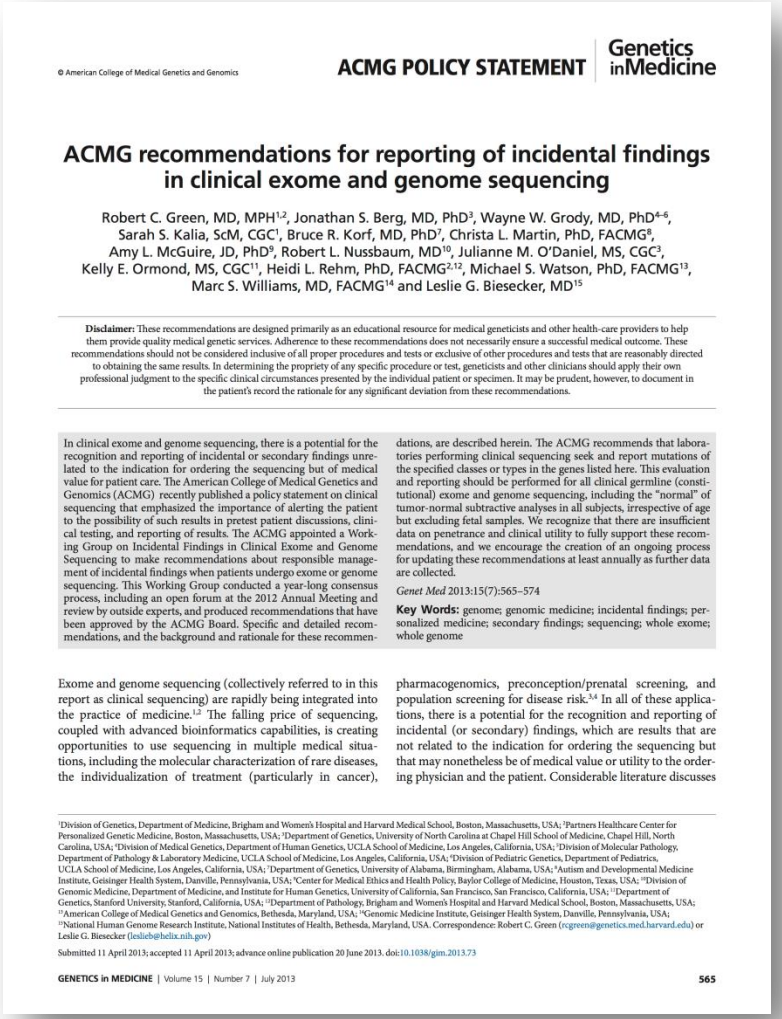
Consent based on sequencing plan

- Tumor sequencing alone
  - Generally no consent done
- Tumor sequencing, subtracting out the germline
  - Short consent, if only returned if germline mutation found during QC process (unusual in the process)
  - Consent required if option to give the germline data back as part of a research protocol
- Tumor sequencing with planned return of germline results
  - Consent required
  - Need to consider extent of germline results returned, e.g. just cancer susceptibility genes or other medically actionable genes as well

Incidental-ome

- Mutations and variants in genes unrelated to the phenotype being studied
- Focus is on medically actionable genes
  - e.g. *LDLR* mutation (familial hypercholesterolemia) in patient sequenced for a brain tumor
- Autosomal recessive carrier status
  - e.g. *CFTR* carrier status
- Pharmacogenetic metabolism variants

"This evaluation and reporting should be performed for all clinical …sequencing, ***including the "normal" in tumor-normal subtractive analyses*** in all subjects, irrespective of age…"



ACMG POLICY STATEMENT | Genetics inMedicine

ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing

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In clinical exome and genome sequencing, there is a potential for the recognition and reporting of incidental or secondary findings unrelated to the indication for ordering the sequencing but of medical value for patient care. The American College of Medical Genetics and Genomics (ACMG) recently published a policy statement on clinical sequencing that emphasized the importance of alerting the patient to the possibility of such results in pretest patient discussions, clinical testing, and reporting of results. The ACMG appointed a Working Group on Incidental Findings in Clinical Exome and Genome Sequencing to make recommendations about responsible management of incidental findings when patients undergo exome or genome sequencing. This Working Group conducted a year-long consensus process, including an open forum at the 2012 Annual Meeting and review by outside experts, and produced recommendations that have been approved by the ACMG Board. Specific and detailed recommendations, and the background and rationale for these recommendations, are described herein. The ACMG recommends that laboratories performing clinical sequencing seek and report mutations of the specified classes or types in the genes listed here. This evaluation and reporting should be performed for all clinical germline (constitutional) exome and genome sequencing, including the "normal" of tumor-normal subtractive analyses in all subjects, irrespective of age but excluding fetal samples. We recognize that there are insufficient data on penetrance and clinical utility to fully support these recommendations, and we encourage the creation of an ongoing process for updating these recommendations at least annually as further data are collected.

Genet Med 2013:15(7):565–574

Key Words: genome; genomic medicine; incidental findings; personalized medicine; secondary findings; sequencing; whole exome; whole genome

Exome and genome sequencing (collectively referred to in this report as clinical sequencing) are rapidly being integrated into the practice of medicine.[1,2] The falling price of sequencing, coupled with advanced bioinformatics capabilities, is creating opportunities to use sequencing in multiple medical situations, including the molecular characterization of rare diseases, the individualization of treatment (particularly in cancer), pharmacogenomics, preconception/prenatal screening, and population screening for disease risk.[3,4] In all of these applications, there is a potential for the recognition and reporting of incidental (or secondary) findings, which are results that are not related to the indication for ordering the sequencing but that may nonetheless be of medical value or utility to the ordering physician and the patient. Considerable literature discusses

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Submitted 11 April 2013; accepted 11 April 2013; advance online publication 20 June 2013. doi:10.1038/gim.2013.73

POLICYFORUM

POINT-COUNTERPOINT

Patient Autonomy and Incidental Findings in Clinical Genomics

Returning genetic incidental findings without patient consent is misguided.

Susan M. Wolf,[1]* George J. Annas,[2] Sherman Elias[3]

Exome and whole-genome sequencing are rapidly moving into clinical application to aid diagnosis and treatment. However, a startling statement by the American College of Medical Genetics and Genomics (ACMG) may prove to be a stumbling block (*1*). Rather than reconfirming well-established principles of patient autonomy and informed consent that have long applied in medical genetics and in medical practice more broadly, ACMG recommends an abrupt change.

When clinical sequencing is undertaken to look for a "primary finding" (i.e., "a pathogenic alteration in a gene or genes that are relevant to the diagnostic indication for which the sequencing was ordered"), the ACMG calls for laboratories to search for "pathogenic and likely pathogenic variants" in an additional 57 specified genes and report results without seeking patient consent. These "incidental findings" are "results that are not related to the indication for ordering the sequencing but that may nonetheless be of medical value or utility to the ordering physician and the patient." However, the ACMG addresses only "the results of a deliberate search" for specific variants, not other genetic findings discovered unexpectedly, the more common use of the term "incidental findings" (*2*–*4*).

The ACMG calls for clinicians to report the results of the deliberate search for incidental findings to the patient, with no opportunity for the patient to decline unwanted information. The patient's only choice is to decline sequencing altogether, even if medically indicated. The ACMG imposes these requirements even when the patient is a child who has no medical need for these results during his or her childhood. The ethical and legal problems raised are profound. A recent ACMG clarification of this practice statement, in response to concerns, makes the problems worse (*5*). The clarification reiterates that patients cannot opt-out of testing on the 57 genes and now says that failing to report these test results would be "unethical."

Patient Decisions and the Right Not to Know

The ACMG rejects the need for the patient's informed consent to a deliberate search for these incidental findings, claiming that the amount of genetic counseling required would be too great. Yet the report marshals no data to support this conclusion and never considers proposals in the literature for streamlining the consent process when large numbers of genes are evaluated, such as "generic consent," which would allow the patient to consider categories of genetic tests together (*6*). The report also rejects the idea that laboratories should mask analysis of certain genes when there was no consent to search for them or could tailor reports, based on unsubstantiated fears of "unrealistic burden upon laboratories."

"Autonomy protects the patient's right to make a decision different from what the clinician might choose."

Rejecting the need for the patient's informed consent to look for mutations in a predetermined list of 57 genes is a profound departure from prevailing law and norms. Informed consent is a well-established legal requirement designed to protect patient autonomy—not a matter susceptible to modification by experts in human genetics, no matter how learned. Circumstances in which clinicians can test without consent are rare exceptions. In a medical emergency that prevents seeking consent—for example, when the life or health of an incompetent or unconscious patient is in imminent danger, and no one is available to consent—society allows physicians to treat without consent (*7*). However, this does not apply when laboratories and clinicians perform clinical sequencing, because they are not responding to a medical emergency threatening imminent harm and preventing them from seeking consent.

ACMG suggests that their recommended search for incidental findings is analogous to a radiologist spotting and reporting an unexpected tumor or other finding of concern on an x-ray. The analogy is misplaced. A deliberate hunt on a predetermined list of genes unrelated to the diagnostic reason for which sequencing was ordered is very different from the unexpected finding of a tumor in or near the area of primary concern in the field imaged by an x-ray. Patients would have no reason to expect a hunt for incidental findings in the 57 disparate genes on the ACMG list, especially when the list includes genes whose analysis and reporting have long required patient consent.

The ACMG is mistaken in basing their search and disclosure recommendations on a "fiduciary duty" to prevent the harms these findings may suggest. In both ethics and law, the clinician has a core fiduciary duty to respect the patient's right to decide what testing to undergo and what information to receive. Patients have an established right to refuse unwanted medical tests and the information they might disclose, even if that information would offer potential medical benefit (*8*, *9*). Indeed, the ACMG has recently affirmed the right to refuse unwanted incidental findings in clinical genomic sequencing (*10*). If the ACMG is now worried about potential liability for failing to return results from their list, they should urge clinicians to document the patient's refusal, not strip patients of the right to decide. Inflicting unwanted information on patients carries its own risk, as unwanted information may lead to anxiety, further clinical workup, and potentially burdensome interventions.

The ACMG's "minimum list" includes mutations in genes that patients have long been able to refuse testing for, including cancer risk mutations (such as *BRCA1*) and cardiovascular risk mutations. There are many circumstances in which a patient may decline such testing and information, even if the results could open avenues for intervention. The patient may already be battling another disease, such as advanced cancer, or be late in life and see more burden than benefit in

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Courtesy of Mark Robson, MD

“Recalibration”

- ACMG Press Release (1 April 2014)
  - “There has been significant discussion surrounding the initial ACMG recommendations…[The board] has recommended that such an ‘opt-out’ option be offered…”
- Not clear how to elicit preferences for germ line “opt-out” in setting of tumor profiling

Conclusions

- Longstanding issues in genetics continue to be discussed in the context of tumor/normal sequencing
  - What are our ‘duty to seek’ and ‘duty to warn’?
- Somatic mutation sequencing at any institution needs to be developed in concert with attention paid to how germline data will be dealt with and returned
  - Each institution may deal with these issues differently
  - Different approaches particularly between whether somatic sequencing comes from an oncology-based or genetics-based laboratory
- Important to have considered questions of consent and data privacy ahead of time and have a **plan**