Using genomic information in clinical oncology and cancer research

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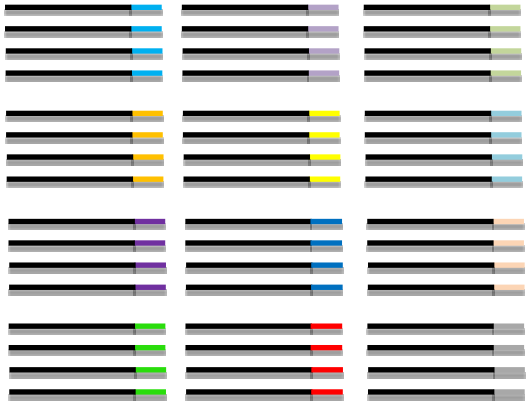
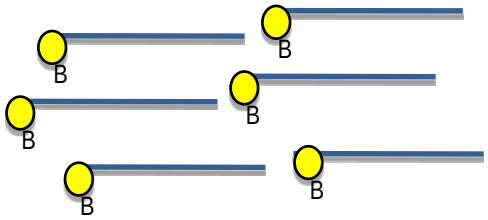
The New Cancer Treatment Paradigm

IMPACT: Integrated Mutation Profiling of Actionable Cancer Targets

Prepare **24-48 libraries**



Probes for **340 cancer genes**



Hybridize and select
(NimbleGen SeqCap)

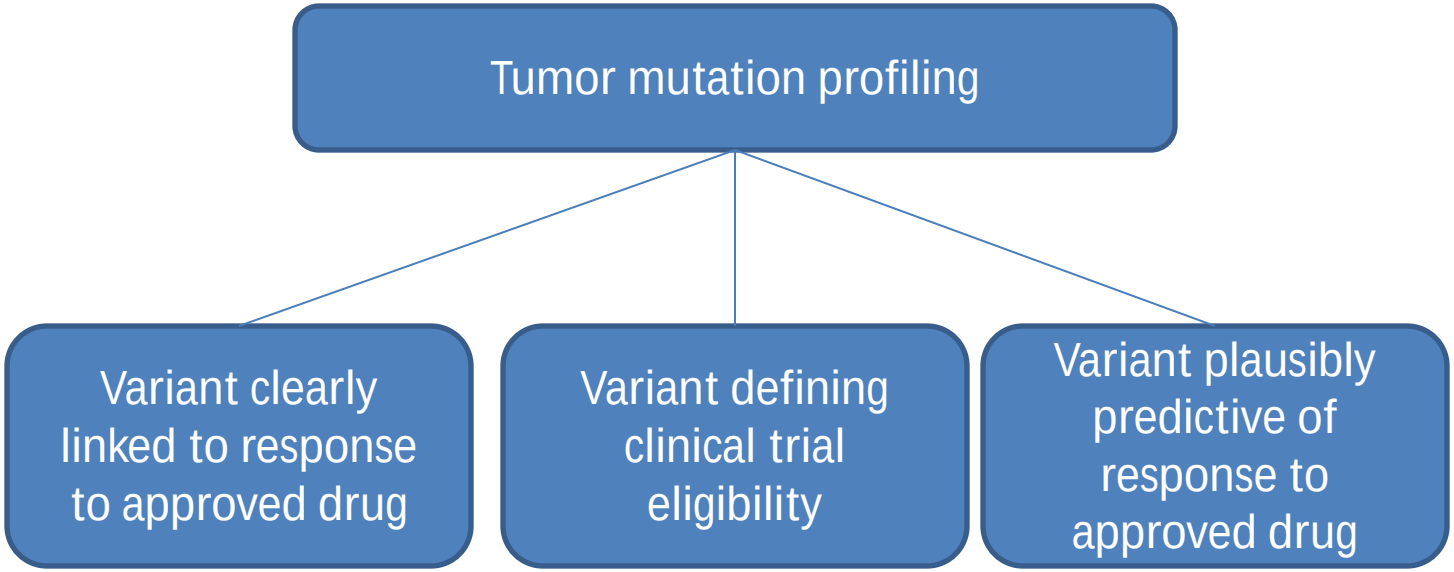
Sequence to 500-1000X
(HiSeq 2500)

Align to genome
and analyze

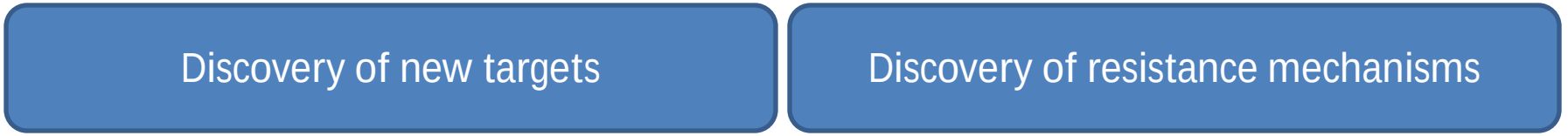
Adapted from *Wagle, Berger et al., Cancer Discovery, 2:82-93, 2012*

Somatic Mutations (Tumor-Normal Pairs):
Base Substitutions
Small Indels
Copy Number Alterations
Select Rearrangements

Clinical enterprise



Research enterprise



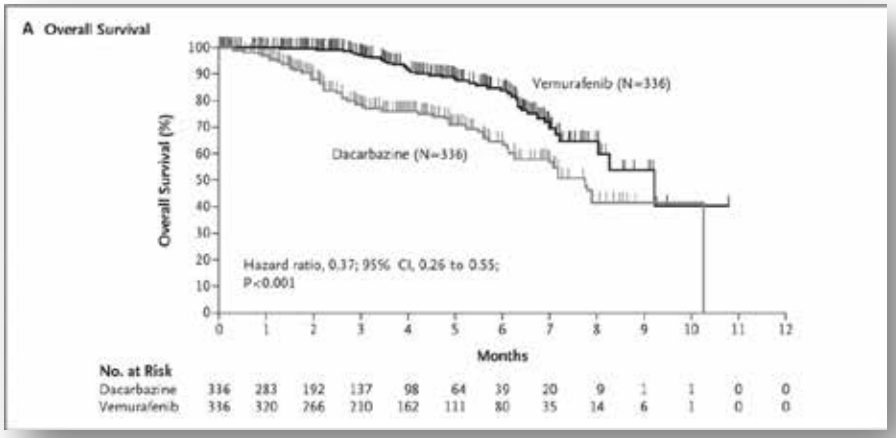
Tumor mutation profiling

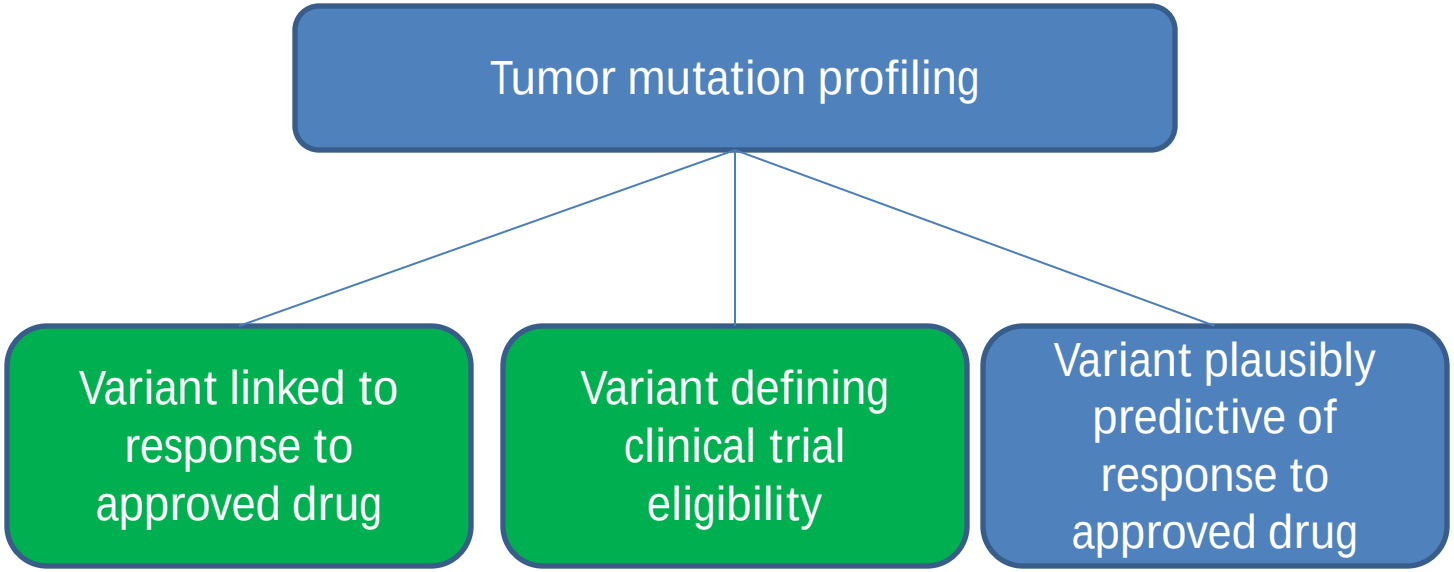
Variant linked to response to approved drug

Variant defining clinical trial eligibility

Variant plausibly predictive of response to approved drug

Companion diagnostic

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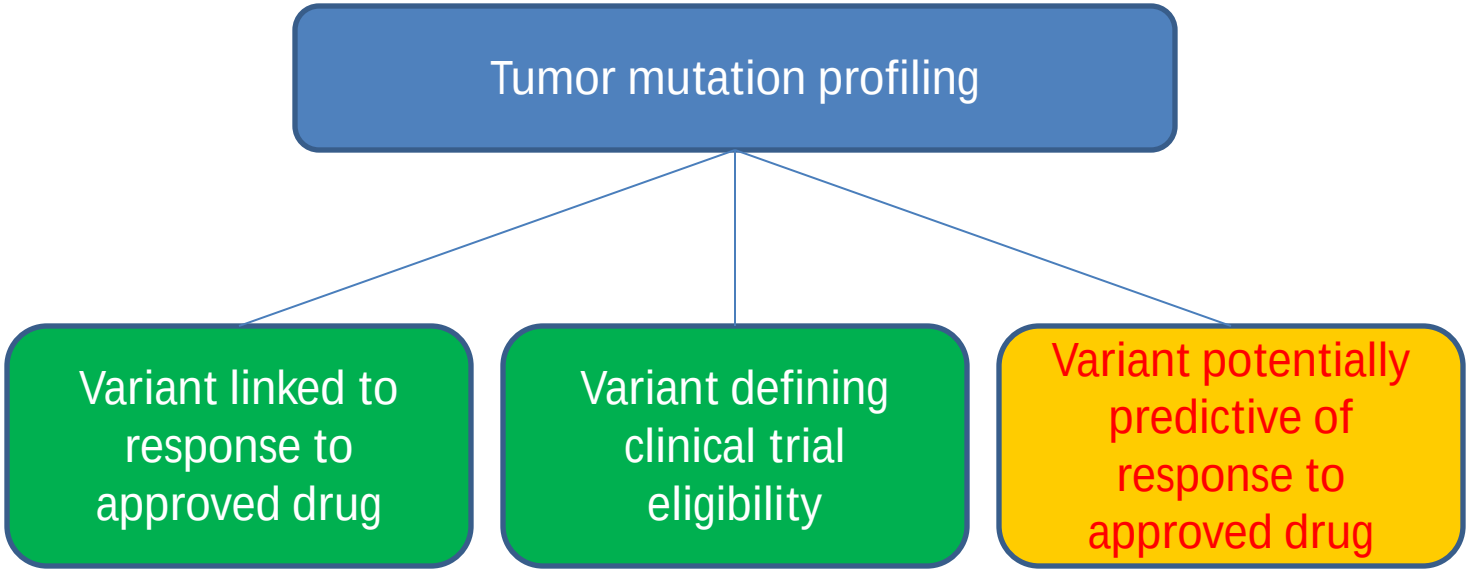


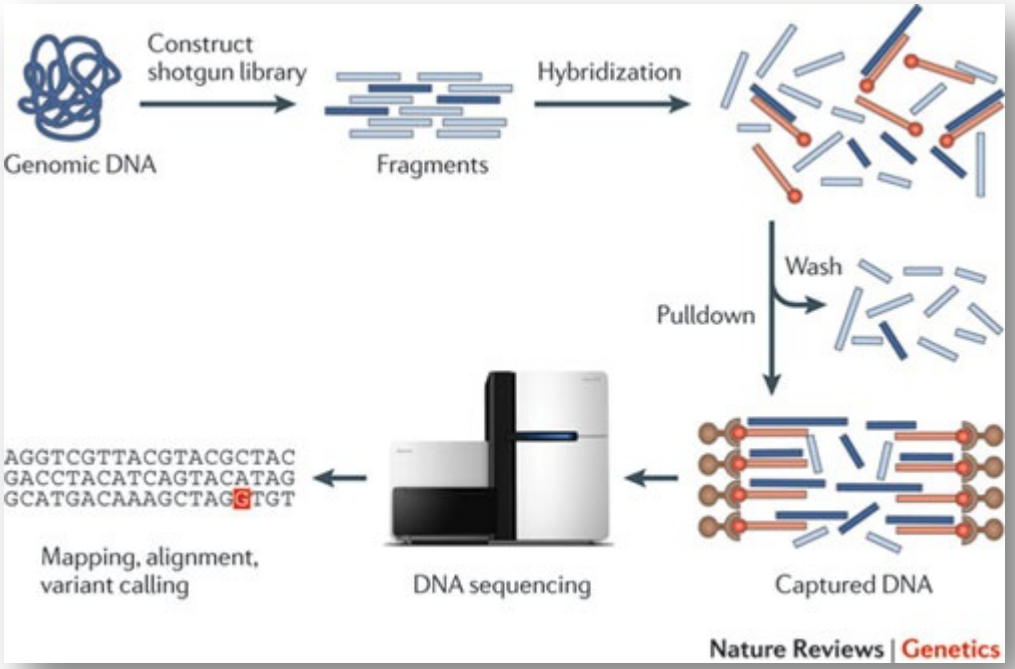
Germline v. somatic
Biologic plausibility
Allele prevalence
Primary v. met analyzed
Availability of drug

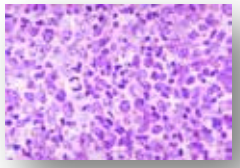
Mechanisms for review of actionability

- Center for Molecular Oncology
- Center for Mechanism-Based Therapeutics

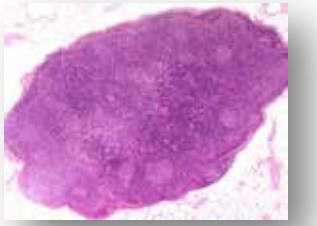
Multidisciplinary panels with expertise in basic science, drug development and clinical trials, assay development and interpretation, computational biology and biostatistics

Optimal Next Generation Sequencing of Tumors Also Means Sequencing of "Normal" Tissues

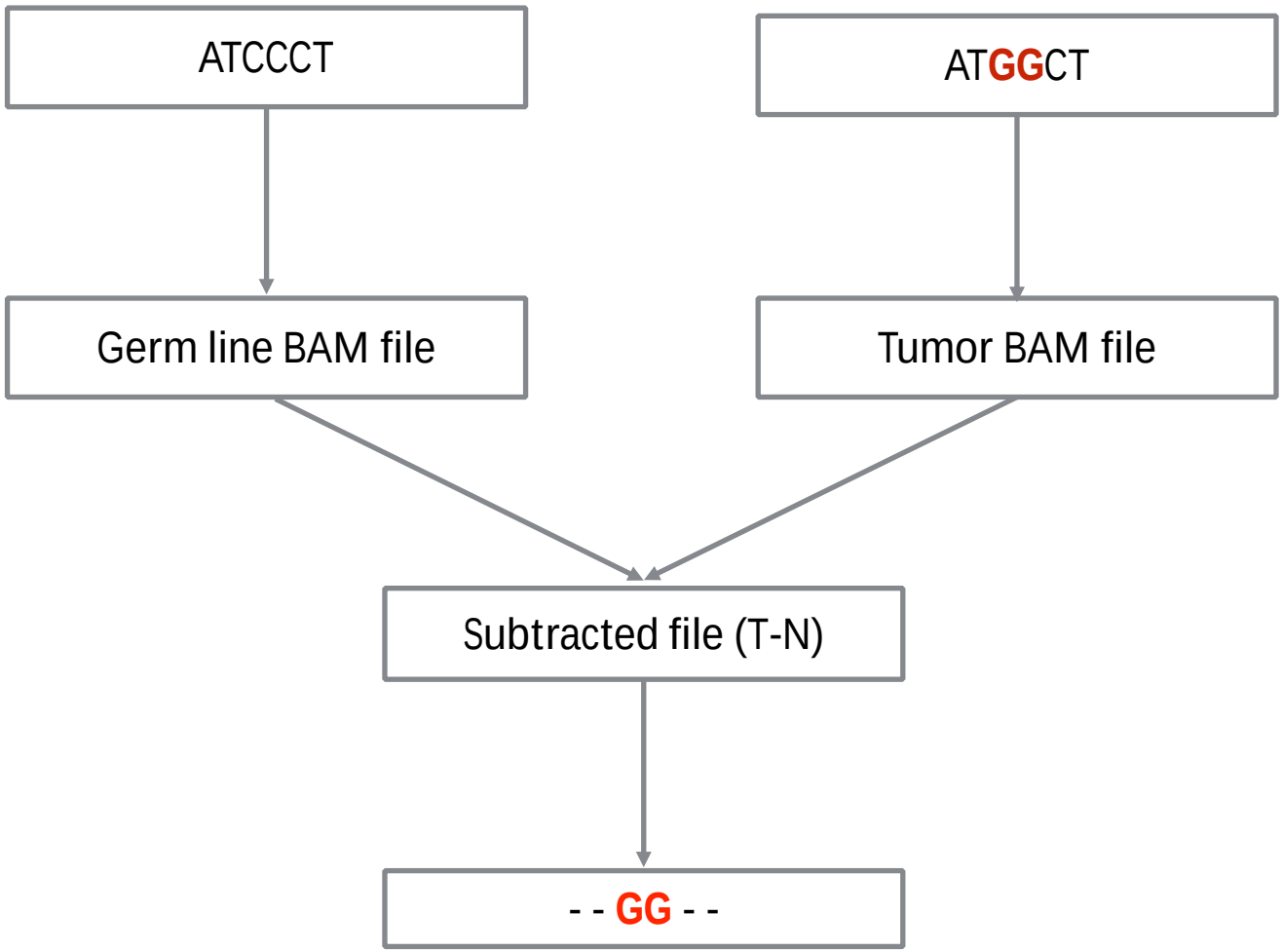




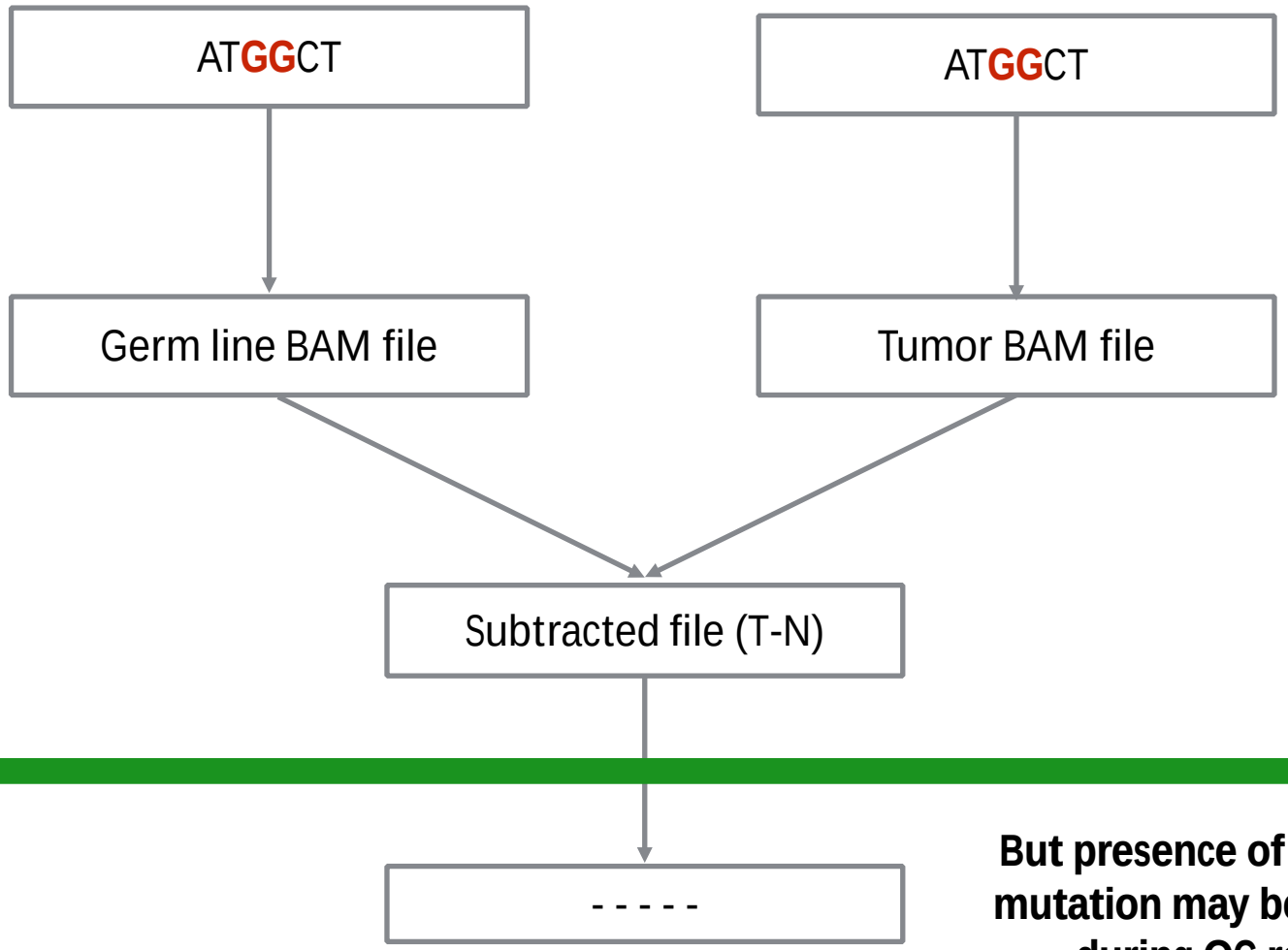
Compare Tumor vs NORMAL tissue



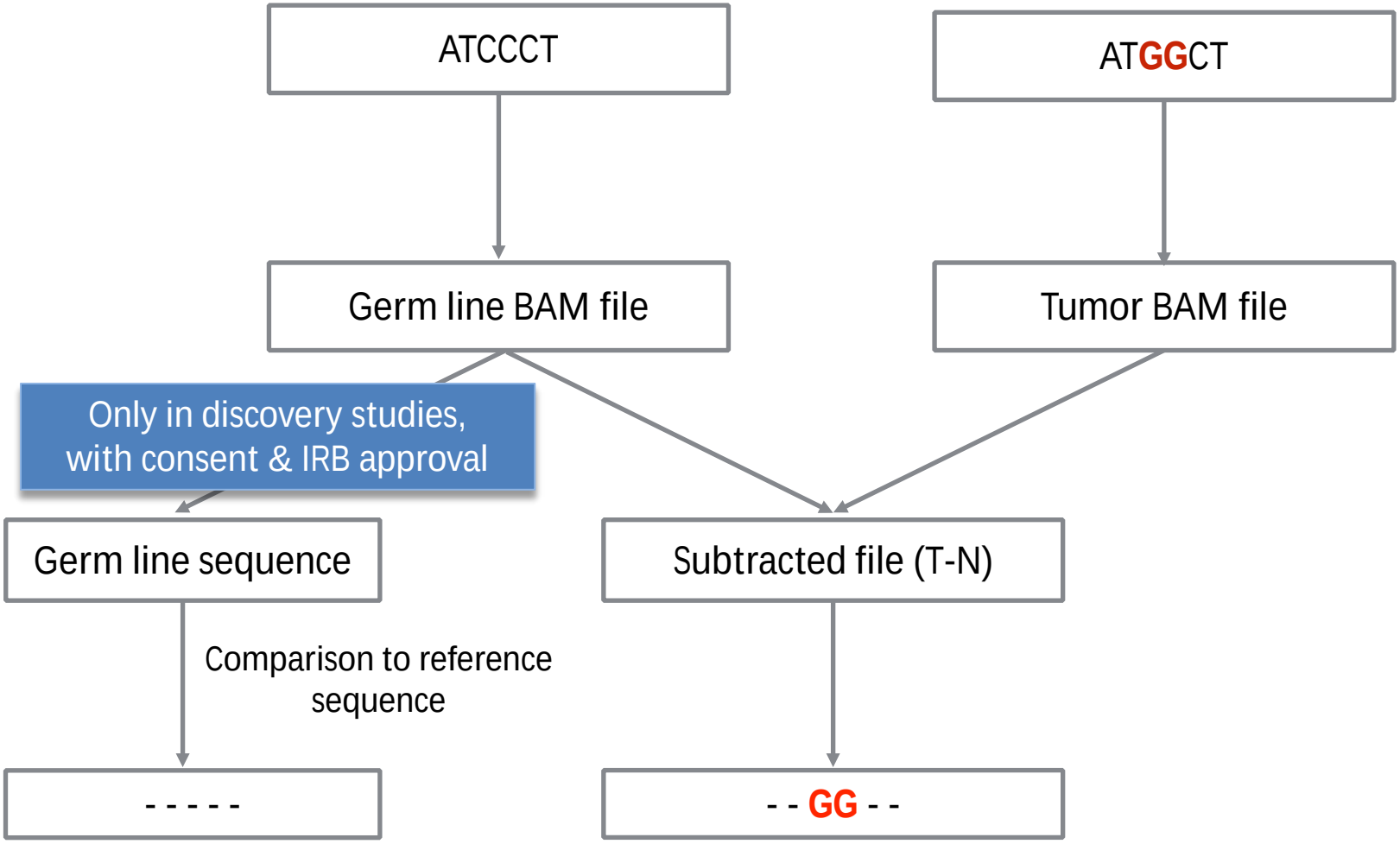
Identifying somatic sequence variations in cancer



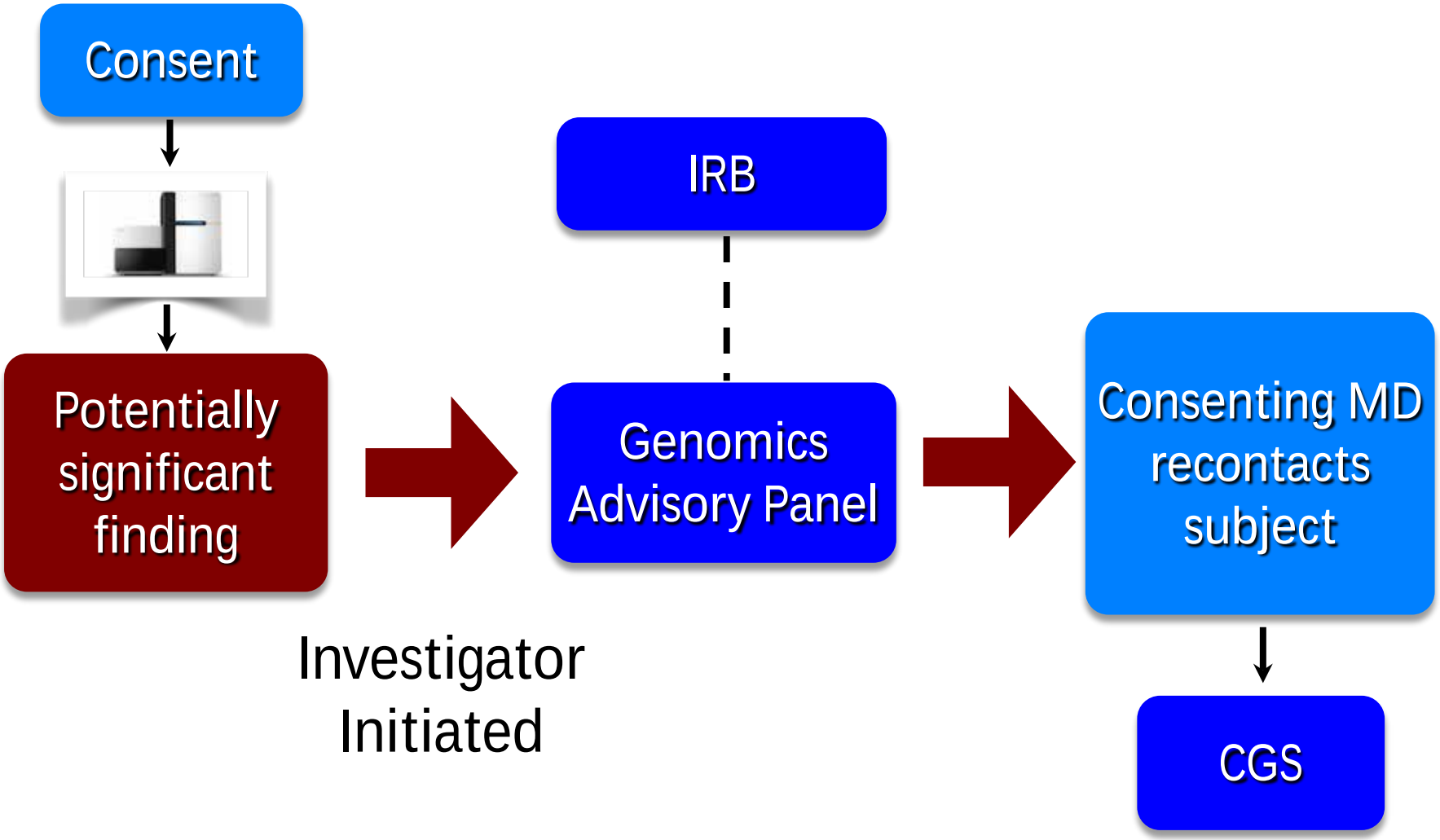
Germline mutations are filtered



Generating incidental findings in tumor profiling



Approaches to deciding on return of results



Summary

- Tumor profiling through NGS primarily designed to identify genomic variations that are already known to be linked to treatment response or that meet pre-defined criteria for clinical trial entry (*a priori* actionable)

- Use of somatic profiling to define off-protocol, off-label treatment is investigational

- Germ line incidental findings in NGS tumor profiling are either indirect (reflected in tumor sequence) or require an active search (“secondary findings”), and are evaluated for actionability by consultation