

Cancer Genome Biology at the Broad Institute: A “Team of Teams”

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Overarching Goals of Broad Cancer Genome Characterization Efforts

- A complete catalogue of significant and impactful tumor genomic alterations
- To address major questions in cancer biology using genomics
- Clinical applications of genome sequencing data

Platforms Leveraged by Broad Research Teams

- Biological Samples Platform
- Chemical Biology Platform
- Genome Sequencing Platform
- Genetic Analysis Platform
- Imaging Platform
- Metabolite Profiling Platform
- Proteomics Platform
- RNAi Platform

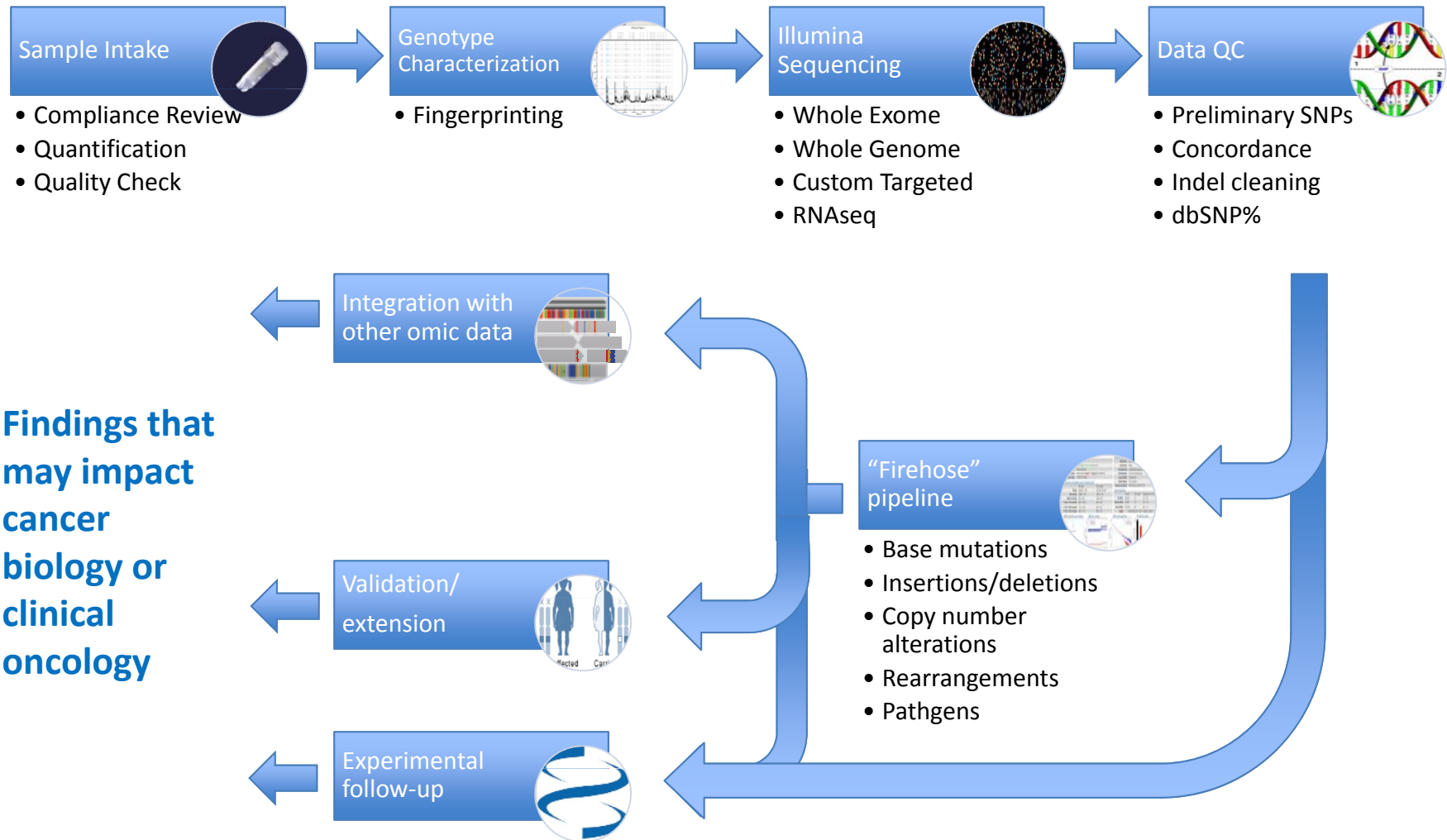
Cancer Genome Characterization at the Broad Institute: The “Core” Team

- 3 Senior Associate Members (faculty)
- 4 Associate Members (faculty)
- 4-6 Research Scientists
- >20 Computational Biologists
- >20 Postdoctoral fellows/students
- Many technicians, project managers, software engineers, etc.
- Many collaborators

Characteristics of Cancer Team Science Projects at the Broad Institute

- Many cancer genome projects, large & small
 - TCGA (GCC and GDAC)
 - NHGRI Sequencing center-initiated projects
 - Broad faculty-driven initiatives
 - Collaborator-driven initiatives
 - Academic-industry collaborations (e.g., CCLE)
 - “Clinical sequencing” projects
 - Philanthropic projects
- Considerable breadth and diversity of genomic data
 - Whole genome, whole exome, “targeted” exome, transcriptome (“RNA-seq”), methylome...

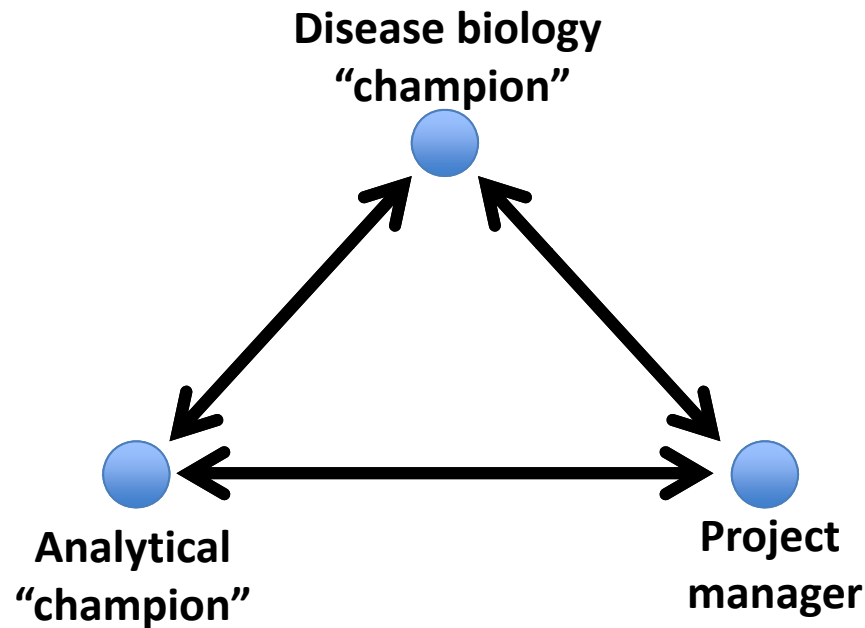
Cancer Genome Sequencing Process Flow



Cancer Genome Projects: Specific Hurdles to Overcome

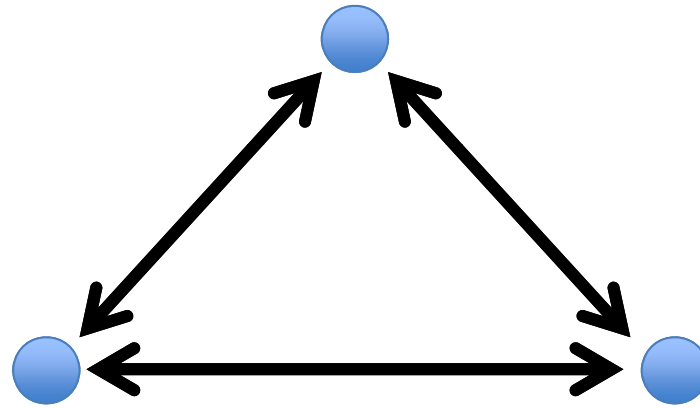
- Process oversight and “de-mystification”
 - Who controls the queue/timetable?
- “Lost in the ether”
 - What happened to my samples/data?
- Production-level “admixture”
 - WGS on Monday; WES on Tuesday, RNA-seq on Wed...
- Bureaucratic and logistical delays
 - Shifting consent form criteria, personnel absences, etc.
- Managing computational bandwidth
 - 1 TB per 60X T/N pair (whole genome)!
- Efficiency of mutation validation/extension
 - We need 200 more T/N pairs now!
- Publication/authorship considerations
 - Who gets to be 1st and last on this 60+ author paper?

Cancer Genome Projects: The “Operational Unit”

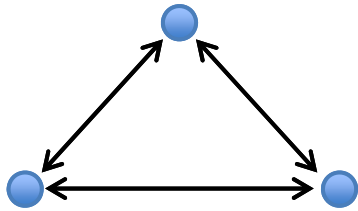


- A triad of “champions” owns each project
- Disease biology: often postdocs, grad students
- Analytical: both post- or pre-PhD with supervision
- Presumes dual first and senior authorship

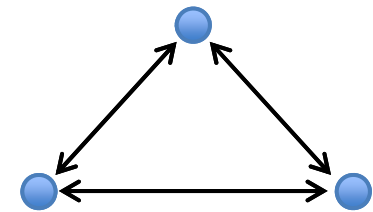
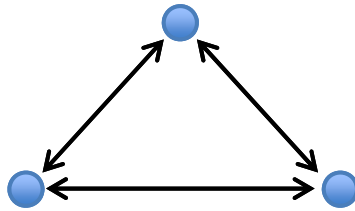
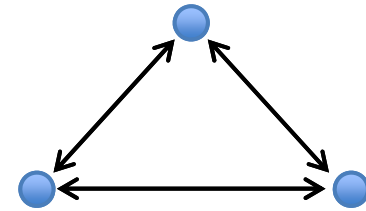
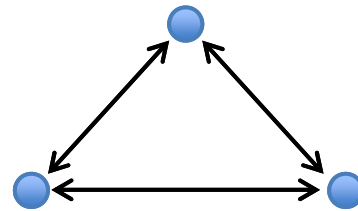
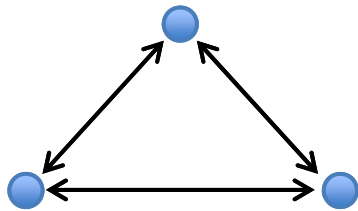
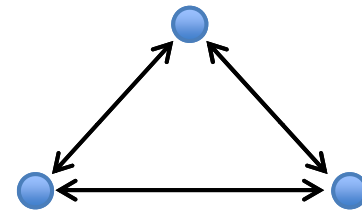
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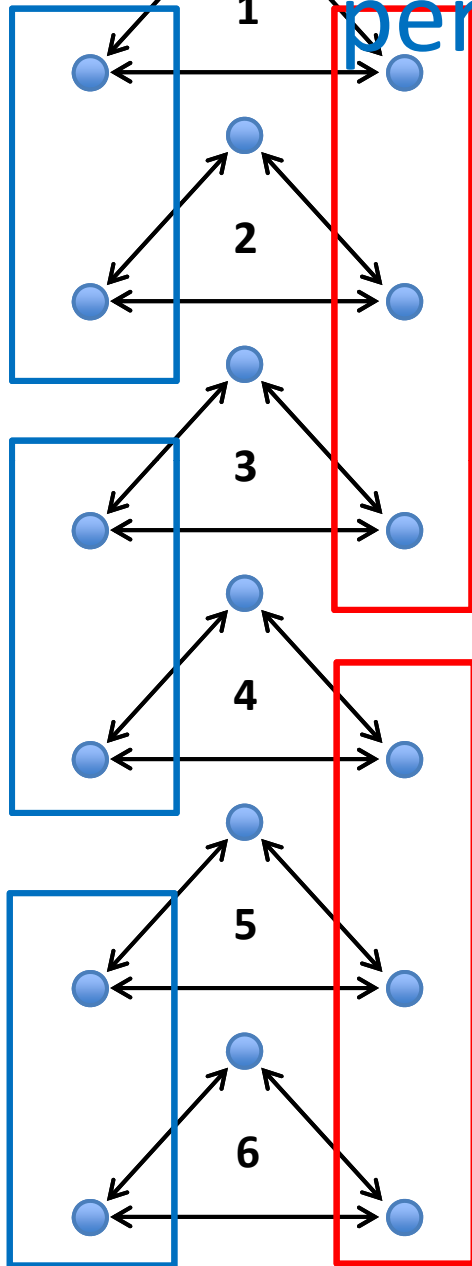
Cancer Genome Projects: The “Operational Unit”



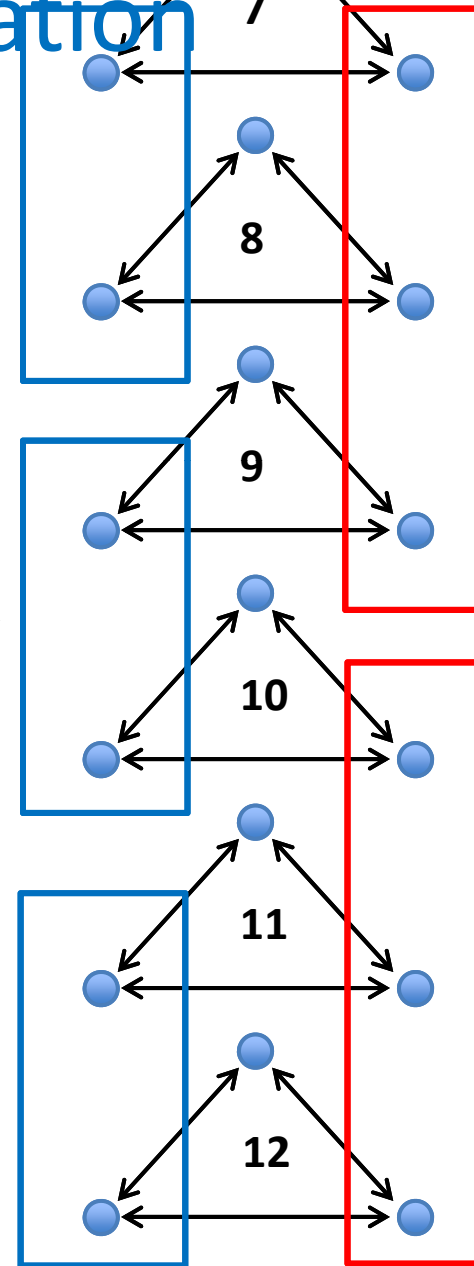
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Phasing increases efficiency of personnel utilization



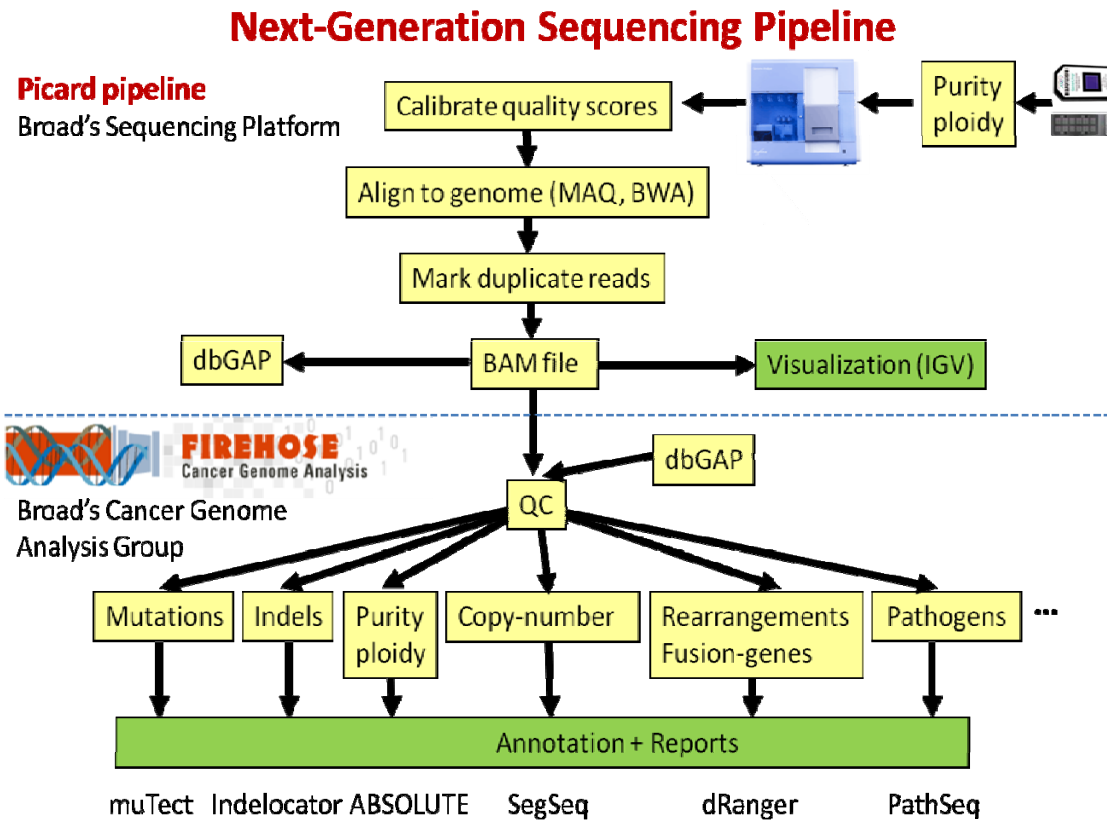
~months



The Cancer Genome Steering Committee

- 4 faculty, 6 staff scientists (2 co-chairs)
- Strategic >> operational guidance
- Scientific input at project “pivot points”
 - (e.g., experimental plan after a key genomic insight is made)
- Identification of systematic errors/issues
- Resource management

Cumulative Cancer Samples Sequenced at Broad



Output (past ~2-3 years)

- ~60 papers (several others submitted/in press)
- >5000 cancer genomes
- Multiple new sources of funding
 - NHGRI Sequencing center grant renewal
 - U01 in Exploratory Clinical Sequencing (with help from NCI)
 - Other R01, U01, P01, R33 grants
 - Multiple foundation grants
 - Industry-sponsored research
 - Other philanthropy

Framework for vetting and prioritizing the next wave of large-scale projects?

- Compelling scientific rationale
- Potential for high impact (scientific or clinical)
- Deeply invested collaborator(s)
- Local “champion”
- Technical feasibility (e.g., the samples are ready to go, the consent form is kosher, protocol active)
- Validation/follow-up plan
- Funding is in place

Flagship Project Concept: (Prostate Cancer, early 2011)

Relevance: biological insights of importance?	
Timely, opportunity	Yes
Address key biological or clinical questions	Indolent versus lethal disease; resistance to antiandrogen therapies, relationship between somatic genomics patterns and ancestry
Systems in place for such questions	Yes
Study Design: comprehensive in breadth or depth	
Ability to expand to multi-dimensional genomics	Yes
Discovery cohort in place	Nearly 300 samples in place, most are frozen tissue
availability / access to extension cohort	Extensive collaborative network in place, both FFPE, frozen tissues and derivative cells
Model system – comparative oncogenomics	GEMM systems that model leading genetic/biological drivers
Follow-through: Coordinated efforts /collaborations	
Functional validations	Yes, active and ongoing
Model systems	Yes, established and emerging ones
Path to translation	Extensive translational / clinical-trial investigators engaged
Logistics: funding, staffing	
Funding for genomic discovery	CIP
Funding for extension studies	Sources available (PCF, Movember, DOD...)
Funding for downstream studies	Funded Starr, DOD grants, SPORE application likely, PCF
Faculty champions	Levi Garraway
Biology champions	Sylvan Baca
Analysis champions	Mike Lawrence
Disease experts collaborators	Kantoff/Rubin/Tewari/Balk/Bubley/Taplin

Broad Cancer Genome Sequencing: Lessons Learned for Team Science

- Deep and sustained collaborations are essential
- All parties must “buy-in” and receive due credit
- “Ground level” ownership by nimble teams
- Data generation is the easy part!
- Think like a biologist, act like a CEO/COO
- “Hub” model for team science research?
- High-level team science cannot happen everywhere