2015 Annual TECAC Meeting Minutes

April 17, 2 015

Attendees:

Name	Affiliation/Country
Julia Barthold	A.I. Dupont Hospital for Children/USA
Victoria Cortessis	University of Southern California/USA
Alberto Ferlin	University of Padova/Italy
Jourik Gietema	Groningen/The Netherlands
Mark Greene	National Cancer Institute/USA
Tom Grotmol	Cancer Registry of Norway/Norway
Trine Haugen	Oslo and Akeshus/Germany
Michelle Hildebrandt	MD Anderson Cancer Center/USA
Peter Kanetsky	Moffitt Cancer Center/USA
Kevin Litchfield	The Institute of Cancer Research/UK
Katherine McGlynn	National Cancer Institute/USA
Nandita Mitra	University of Pennsylvania/USA
Kate Nathanson	University of Pennsylvania/USA
Jeremie Nsengimana	University of Leeds/UK
Anand Pathak	National Cancer Institute/USA
Jen Poynter	University of Minnesota/USA
Lorenzo Richiardi	University of Turin/Italy
Trine Rounge	Cancer Registry of Norway/Norway
Stephen Schwartz	Fred Hutchinson Cancer Research Center/USA
Benita Weathers	University of Pennsylvania/USA
Fredrik Wiklund	Karolinksa Institute/Sweden
Tim Bishop	University of Leeds/UK

Meeting Opening

- Caryn Lerman, Deputy Director of the Abramson Cancer Center at the University of Pennsylvania, extended a warm welcome to the TECAC.
- Meeting participants introduced themselves.

TECAC Updates

Study Progress

- Kate provided study progress updates:
  - MTAs have been established with most sites; two sites pending, USC and a new site Princes Margaret.
  - Samples have also been received from most sites; pending are FHCRC and Erasmus. USC and Princess Margaret are pending MTA agreements.
  - We have received a total of 12,651 samples to date
  - 15,000 assays with 8110 SNPs have been ordered and are scheduled to arrive at Penn on May 4, 2015 at which time we will plan to start genotyping the current samples that we have.
  - Of the 3301 SNPs that were submitted, 492 failed and 331 were already on the array, thus a total of 3276 SNPs were requested.
  - Sites that would like to obtain the list of SNPs submitted from their respective institutions should request it of Benita.
  - Collaborators interested in developing manuscripts regarding the SNPs submitted by their sites must submit an analysis concept proposal which must be

reviewed and approved by both the TECAC Steering Committee and Guidance Council.

Phenotype Data

- Katherine McGlynn reported that the majority of expected phenotype data have been uploaded. We are still awaiting phenotype data from Yale, MDACC and some from Oslo
- Michelle Hildebrandt indicated that they have identified the samples they will genotype and, thus will soon have the corresponding phenotype data ready for upload.
- The phenotype data file has been updated for the meta-analysis

Movember

- Kate indicated that Movember is interested in collaborating with the TECAC.
- Movember is a foundation that has as its vision "to have an everlasting impact on the face of men's health."
- Investigators were invited to respond to an expression of interest to receive funds from Movember for research related to men's health. Nine international sites were selected including, Penn (Nathanson), MSKCC (Feldman), TCCC (Nichols), Netherlands (Looijenga), Denmark (Rajpert-deMeyts), Australia (Grimson), DFCI/Broad (Van Allen), and UK (Berney).
- The initial project focus will be on patients who relapse with clinical stage 1 NSGCT using already genotyped patients with outcome data to identify associated SNPs.
- Jourik will take the leadership on this collaboration
- Steps toward moving forward with this project include:
  - Identifying TECAC members who have outcome data and are interested in contributing to that data.
  - Identify those within TECAC who might be interested in participating in a joint governance.
- Victoria asked what the genotyping would be. Kate responded that we will use the same chip with additional samples.
- Kate assessed by show of hands who had the following:
  - Outcome data (dead vs. alive)-Victoria, Michelle, Steve, Jeremie, and Jourik
  - Treatment data- Victoria, Michelle, Kate
  - Relapse data- Kate, Jourik
- We will determine what variables to analyze
- Vicki asked if additional phenotypes would need to go into dbGaP. Kate indicated that since this would be funded with public funds rather than NIIH funds, deposition into dbGaP would not be required.
- Vicki also indicated interest in an opportunity to look at cultural differences and what is attributed to those differences. Peter indicated that would be something to discuss during the working group break-out sessions.

TECAC Analysis Concept Proposals

- Two rounds of concept proposals have been completed and a total of 8 applications have been approved by the TECAC Steering Committee (SC) and Guidance Council (GC). All approved proposals have been uploaded onto the TECAC website. Approved proposals include the following:
  - Genetic variants in aging and developmental pathways as predictors of testicular cancer risk (Michelle Hildebrandt)
  - Validation of cryptorchidism risk loci (Julia Barthold)

- Association study between genetic variants influencing global DNA methylation and testicular cancer risk (Lorenzo Richiardi)
- Assessing the Validity of a Testicular Cancer Polygenic Risk Score in the TECAC GWAS Data Set (Mark Greene)
- Association study between GPCR and nuclear receptor genes for pivotal endocrine regulators of testicular function and testicular cancer risk (Alberto Ferlin)
- Copy number variants (CNV) and susceptibility to TGCT(Kate Nathanson)
- Systems-biology based GWAS analysis with emphasis on pathways and the TGFBR3/BMP networks (Ramneek Gupta)
- Potential impact of genetic loci showing signs of positive selection on the development of Testicular Germ Cell Tumors (Davor Lessel)

- The deadline for round 3 concept proposals is July 1, 2015.
- Kate reminded the group that in order for persons to analyze data related to the SNPs they submitted for the assay design, they **must** first submit a concept proposal for approval by the SC and GC.

Data Access for Secondary Analyses

- Information has been distributed to those who will need access to the TECAC Data Analysis database.
- The data are near ready to upload for analysis.
- A signed DUA needs to be in place before final access to the data is granted.

Reimbursements

- Kate reminded the group to keep all receipts and provide to Benita ASAP
- TECAC will cover one night hotel stay and air fare for those who made special trips to attend the meeting.

Future TECAC Meetings

- While future AACR meetings will be held in New Orleans (2016) and Washington, DC (2017), as well as an Workshop on CIS and cancer of the testis (2018), TECAC members were asked to think of other possibilities for the TECAC annual meeting in addition to those listed.
- The Steering Committee will discuss options further and poll the group at a later date.

TECAC Presentations

- ***Kevin*** presented data he recently submitted for publication entitled *Whole-exome Sequencing Reveals the Mutational Spectrum of Testicular GCT*. Questions asked of Kevin include the following:
  - Vicki- have you compared results of men with bilateral disease and/or undescended testes? Kevin indicated that he did not do an analysis on bilateral disease and did not have data on undescended testes.
  - Jourik suggested doing analyses on those with young on-set, non-seminoma and decease quickly after disease diagnosis
  - Kate inquired about how to deal with admixture (i.e., mixed NSGCT). Kevin was not sure about those details.
- Steve discussed TECAC governance and indicated that he is in the process of making minor revisions to the manuscript guidelines. He also called for members to join the Steering Committee. Kate highlighted the commitment requirements for those who desire to be a part of the SC- participation on one-hour conference calls every two weeks.

- The group pondered who should be considered a "TECAC member" and how to deal with External Advisory Board members who may want to play a larger scientific role.
  - Michelle suggested assessing how other Consortia handle this issue.
  - Mark suggested dealing with it on a case-by-case basis.
- The Steering Committee will ponder more and develop some guidelines to be reviewed by the larger group.

Presentations of Analysis Concept Proposals

- Three TECAC members presented their analysis concept proposals which were approved by the SC and GC. The presentations included the following:
  - Genetic variants in aging and developmental pathways as predictors of testicular cancer risk (*Michelle Hildebrandt*)
  - Validation of cryptorchidism risk loci (*Julia Barthold*)
  - Association study between genetic variants influencing global DNA methylation and testicular cancer risk (*Lorenzo Richiardi*)
- The group broke for lunch after which three more concept proposals were presented, including:
  - Assessing the Validity of a Testicular Cancer Polygenic Risk Score in the TECAC GWAS Data Set (*Mark Green*)
  - Association study between GPCR and nuclear receptor genes for pivotal endocrine regulators of testicular function and testicular cancer risk (*Alberto Ferlin*)
  - Copy number variants (CNV) and susceptibility to TGCT (*Kate Nathanson*)

TECAC Meta-Analysis

- Zhaoming presented his findings to date from the meta-analysis. The main findings include…

TECAC Working Groups

- Peter reviewed the goals of the WG break-out sessions, which were to:
  - Provide input into specific planned U01 analyses
  - Promote and develop new areas of research within the consortium
  - Make plans for goals to accomplish over the next year
- Summary of WGs:
  - ***Associated Phenotypes/Non-Genetic Risk Factors***-(Katherine McGlynn, Victoria Cortessis, Alberto Ferlin, Trine Haugen, Anand Pathack, Zhaoming Wang)-Goals for the next year include:
    - Literature review
    - Assessment of additional phenotype data TECAC members may have, as well as fertility data (e.g., from ultrasound records)
    - Assess whether investigators have pre-diagnostic serum as opposed to post
    - Create a list of genes that are integral to endocrine disruption for an analysis of endocrine receptors
    - Contact other large groups that may have fertility measures
    - Obtain population prevalence and odds ratios from each country for an analysis of population attributable fractions
  - ***Maternal and Parent of Origin***- (Steve Schwartz, Jeremie Nsengimana, Mark Greene, Lorenzo Richiardi, Trine R., Jen Poynter, Tom Bishop, Fred Wiklund) – Goals include:

- Development of main manuscript idea:
    - Analysis of SNPs tested for maternal/parent of origin effects because they are offspring (from meta-analysis and replication) or suggested by prior maternal/parent of origin effect papers.
    - GWAS of remaining SNPs for maternal/parent of origin effects
    - All of the above by histologic type and other characteristics, e.g., UDT status
- Other ideas discussed by the group include:
    - De novo mutations (would need to explore whether we can impute exome rare variants from the GWAS backbone)
    - Maternal effect of candidate SNPs (based on pathways we think are relevant to TGCT etiology)
    - Jeremie's proposal to study interactions between maternal effects (candidate gene based on pathways) and offspring genotype (all GWAS SNPs or known offspring GWAS hits)
    - Tim had the idea of a more direct GWAS of TGCT mothers (cases) and non-TGCT mothers (controls). The non-TGCT mothers would be women for whom GWAS data exist and for whom we feel could be good matches on genetic background for each of the datasets we have. Might this be an ancillary analysis to the main paper GWAS?

- ***Survivorship, Pharmacogenetics, and Outcomes***- (Kate Nathanson, Peter Kanetsky, Kevin Litchfield, Michelle Hildebrandt, Tim Bishop, Jourik Gietema)
    - Study of Stage I NSGCT using funds from Movember to get better phenotypes from this cohort.
    - Vicki suggested querying the TECAC regarding race and ethnicity data and data on relapse referrals to surgery centers. Samples should be a part of the genotyping dataset.
- ***Associated Phenotypes/ Non-Genetic Risk Factors***- (Katherine, Victoria, Alberto, Trine H., Anand, Zhaoming)
    - E-mail sites to assess what other phenotype data are available as we are missing phenotype data from several controls.
    - Ask others to join in who may have the necessary data
    - Review literature
    - Request other fertility related data, e.g., from ultrasound records
    - Assess if people have free diagnostic serum as opposed to post
    - Give analysis of endocrine receptors
        - List of genes important in endocrine disruption
    - Contact other large groups with fertility measures
    - Conduct an analysis of population attributable fractions- will need population prevalence and odds ratios from each country