GeM Consortium
Genomics of MPNST

11/29/17 – Meeting Minutes

Genomics & Informatics and Oncology & Pathology Joint Meeting

Meeting Attendees:

David Miller (Boston Children's Hospital), Angela Hirbe (Wash U), Jack Shern (NCI), Nischalan Pillay (Royal National) , Nimesh Patel (Lifespan), Marilyn Bui (Moffitt), Justin Guinney (Sage), Sonika Dahiya (Wash U), Mike Lawrence (Broad), Brendan Dickson (Mount Sinai), Marilyn Bui (Moffitt), George Charames (Mount Sinai), Jesse Hart (Lifespan), Adrienne Flanagan (Royal National)

- **Data Analysis Plan**
    - DM: What are the approaches we might take? What are the strategies we could use at an analytical level related to certain clinical questions? I think one of the research questions we have is genomic discovery, molecular or biomarker characterization of tumors as it relates to certain clinical endpoints. There are various approaches in terms of whole genome vs exome and other types of analyses.
        - AH: We should collect as many triads…plexiform and normal from each patient
        - DM: If we have these triads of multiple tumors of different stages of progression. What would we consider the optimal analysis strategy?
            - DM: Would we want to do deeper than standard whole genome sequencing? Would we do a much deeper exome?
            - JS: I think if all we are going to have is FFPE right now, whole genome will be very challenging, but a whole exome is very doable in terms of archived samples. Unless you have a lot of fresh frozen, whole genome may be difficult to interpret right now.
            - DM: We can do epigenomic profiling for FFPE. Nischalan was suggesting there are some cases based on fresh frozen to do RNA-seq Chip-seq, bisulfite-seq.
    - DM: We all have similar ways of looking at approaches we might take. I am wondering if the next step is to take a more detailed survey of what cases we already have banked – and the characteristics of those samples - are they fresh frozen, are they FFPE, what was the pathology of them? We can see if we have 25 cases of a certain type, and for example…how many samples taken from the same individual? What would be the next step to move this forward?

- SD: We can see how many frozen samples are available at each institution. FFPE would be easier to retrieve, but frozen tissue is good to start with in terms of progression.
- DM: Should we make a web-based survey to get more information about what kinds of samples are out there? We can work on creating a more detailed web-form to see what kinds of samples people have.
    - SD: I think this will be helpful in terms of having a good strategy moving forward.
    - DM: We should also discuss the issue that there are values with doing whole genome, but in terms of tumor heterogeneity, we may want to do several samples from the same tumor and we may do whole exome coverage (where whole genome's just wouldn't be feasible.

- AF: Pulling the samples together is of critical importance. Do you need a pathology fellow to coordinate that? This will be very time consuming.
    - DM: I have two full time people here (study coordinator support) and we have Alyaa Al-Ibraheemi who is pathology junior attending here at Children's who will help with coordinating.
        - AF: This is almost a full-time job. If you want uniformity, you would need funding for someone to do this – someone who is pathology trained.
            - DM: Specifically you mean someone who has had pathology training?
            - AH: That is why we have the SOP for the Pathology Review.
                - AF: But in the pathology review, you have Fletcher and Petur who are senior pathologists – we would need a fellow to take this on as a major project.
                    - DM: I will talk more with Alyaa about this.
                - DM: I am not sure how many people will be sending DNA/RNA vs tissue, but I don't want to underestimate the amount of effort put into this.
                - AF: I think this is a nice project for a trainee pathologist.
                - DM: We will make sure Alyaa connects with pathologists on this call to more clearly outline handling these cases.
                    - AF: We need to do this really comprehensively and this is a huge time commitment for an individual. We need a PhD or MD student to take this on as a project.
                    - BD: I agree with Adrienne's comments. We have a wealth of frozen tissue and a wealth of FFPE, and coordinating everything is a huge amount of work.
                - DM: If we have a person who is at the trainee level here in Boston, is that going to meet the needs you are

talking about? I still think there is a lot of effort put forth by pathologists at institutions. We need to figure out how many pathologists will be involved. We were going to do this on a per sample basis – perhaps we can adjust for people's time commitments.

- DM: I am not sure if someone added to the coordinating center would solve this problem. If we had estimates for costs of reimbursement on a per sample basis
- BD: I think she is looking for one point person in particular. I am not expecting any compensation for my efforts.
- AF: We can give this further thought.
- DM: If anyone has any ideas about how to appropriately offset these types of efforts, please email me.

- DM: Mike Lawrence from the Broad is on the call – he does a lot of cancer genomic analysis. I think it would be good to have discussion about numbers of tumors – at what depth, whole genome vs. whole exome depending on what types of samples we have available. Are there ways to think about doing a pilot approach for multiple ways and having an intermediate re-assessment of approaches.
    - AF: That sounds sensible to me
    - DM: What would be a good starting point if we were to do a certain number of samples of fresh frozen and paired normal and if we were to do exome vs genome sequencing – or if we were going to sequence five sites per tumor and the tradeoffs of doing it genome vs exome.
        - ML: Genomes cost a little under twice as much as exomes. The deep coverage of whole exome sequencing would be very good to have. This tumor type has a very low background mutation so this works in our favor for finding significantly mutated genes. If we had 100 patients, we would have 90% power to find genes mutated in at least 10% of patients 33% power to find genes mutated in 5% of patients. We can revise this calculation to consider larger cohorts. It is difficult to say because we aren't really sure what we are looking for.
        - DM: My assumption is that we would have to sequence tens or dozens of tumors before we could do any preliminary analysis and feel confident that if there was something there, we would be able to find it – in terms of changing approaches.
        - ML: The landscape of the major driver genes is already established. To get beyond that, we need more patients. For looking at multiple sites per patient, that is more wide open. So far we've only looked at one patient – 2 samples from the patient. We don't know if this will be representative of patients in general as we start looking at additional patients.
        - DM: Jack, what do you think would add the most value right now?

- JS: I would echo the last comment. I am not sure that the goal of this should be to identify new drivers that occur in maybe 3% of MPNSTs. We should be thinking about heterogeneity and how the tumors may be progressing – as opposed to getting as many tumors as we can and sequencing them like other institutions have.
- AF: I support that. This depends on months of selection of cases – it's this detail that will allow us to get the data
- AH: The heterogeneity question is very interesting. I still see some advantage of looking at the progression of plexiform – not just at the exome level but also epigenetic changes. Something else may be driving this transition
- DM: We talked about trying to identify cases with different stages of lesions
- AH: We need to decide what we are going to go after. We shouldn't go ad sequence as many cases as we can the same way that Hopkins of MSK has done.

- DM: What would be the best way to create a CRF for cases everyone has banked? What are the data fields we need? I would like to begin process of getting a survey of cases banked and the characteristics of the cases.
- DM: Looking at same type of tumor but at different anatomical locations – whole genome vs exome – whether we would need to sample multiple sites per tumor? The main difference is that since whole exome sequencing is cheaper, we can do it at a greater depth.
- DM: Would people generally agree that we might be better off with higher depth exome with copy number included, epigenetic, and may include transcriptome (may be less reliable for FFPE)?
    - SD: I agree.
- DM: What we should do next – survey for more information about cases everyone has banked already so that we can formulate a plan around this. Is this a workable plan? We wouldn't want to leave out important features for our survey.
    - AH: We don't need all the clinical information.
    - JS: We need to set what the bank is. Until we can talk about assays, we need to set what the bank is and define it. The key question – is it frozen or FFPE? If it's FFPE, do you have 2 slides or a whole block? What is the diagnosis? Include pathology report.
    - DM: I am trying to make sure we ask all the relevant questions but a small set of questions.
        - AF: We can do a small pilot of collecting data – maybe 10 cases. We don't want to spend weeks on this to find we have left out a critical question.
        - AH: We can list cases - FFPE or fresh frozen or both, how many sites, blocks from multiple sites if FFPE or one site, pre or post treatment, site of the tumor.
        - MB: We can do a quick inventory to see what we have, but moving forward, we need to collect in a uniform, standardized format.

        - AF: We can send out a simple excel file – every group would put in 5 or 10 cases – everyone will look at it and decide if we should modify.
- DM: I'll propose that we can put the Excel sheet together and try and get short-term feedback to see if anything was left out – if everyone can look at it by early next week. We can send it around again and collect a few cases from each site as a pilot approach (what Adrienne suggested).
    - Everyone in agreement
- DM: On the most recent SC call, we discussed how it would be ideal to elect a chairperson (other than David) for each working group. If people are interested in this role – run meeting, set agenda, moderate discussion for WG – please email us. We will cover their travel for the April in-person SC meeting. We can gather all the names and discuss this at the next SC meeting. We will be in touch soon with the Excel sheet.