SAB FHU TRANSLAD meeting (December 5, 2018)
GENERAL REPORT AND RECOMMENDATIONS

The members of the SAB first wish to congratulate the coordinators and all the members of the team. The amount of work that has been performed, the clinical impact, the number of activities and publications, and the scientific output , the reach out to the patients and the public, all is impressive. Actually, the team has done more and reached further milestones than those that had been put forward in the project. The team is enormously dynamic, and the realm of their activities is very broad. The clinical and societal impact of the work is significant.
The team has responded very well and very adequately to the observations and suggestions made during the previous SAB meeting.

Below is a list of comments and considerations, not necessarily in the order of importance.

1. The first aim, from a clinical and diagnostic standpoint, was clearly to shorten the diagnostic odyssey of a patient. It was definitely controversial at the starting date of the project to stop classical genetic testing, in favour of moving straight to the most comprehensive NGS application, i.e. the exome. Now, this approach has proven to be the correct one, the team clearly had made the right choice. In addition, the model has been taken up by other centres (Lyon was mentioned as one of them).
2. The patients and families are the ones that should benefit from the integrated service that is offered by a genetic centre. It is clear that they are indeed the focus of the activities of the team. The frustration of patients, parents and care takers is with the delays in testing. The team has adequately responded to this.
   The focus has been broadened to other medical specialities and the laboratory offers diagnostics beyond multiple congenital anomalies and intellectual disabilities. There I also an interest to include adult patients (neurological, familial cancers and atypical chronic diseases).
3. The re-analysis of data has yielded interesting data. There has been an 8% in the detection rate, by re-analysing the genomic data annually. The team has been internationally recognized for this study (published and presented at high level conferences).
   Also, the participation of the team in international initiatives like MatchMaker, to increase the clinical yield, is interesting. Clearly, the team constantly re-evaluates existing data and novel approaches for data mining. This proves that the team is using cutting-edge tools for clinical practice.
   Many publications witness the leading role of the team is the promotion of genome diagnostics.
4. There is an interest in fast prenatal NGS diagnostics. A study, in the context of the network (filière) (i.e. AnDDI-Prénatome) received special attention. It comes with all the challenges of fast, genomic analyses. Similarly, there is a project to sequence neonates. The team is clearly in a good position to address these challenges, and shall further invest in these approaches.

5. The numbers that are available, are impressive: for instance, the team has grown very quickly to about 35 people. The latter was seen, both by the SAB as by the team

leaders, as the biggest challenge: how to warrant employment for all the collaborators in the future. Hence there is a need for investment in permanent staff.

6. In the report, detailed figures (données chiffrées) on the clinical activities are lacking. Hence, for some aspects, it is difficult for the SAB to grasp what has exactly been going on.
7. The overall financial balance (bilan) is good, the investments have led to the creation of a clinical and diagnostic service that is operational and performs well, with a close interaction between basic and clinical research, in Dijon as well as in the associated centres.
8. The SAB has hinted at the question whether there are hidden costs contributing to the project. The latter is essential as they are important for the calculation of the real cost of the services. It would be good to have at least an idea.
   This issue popped up specifically in the context of whole genome sequencing: who takes care of the costs of the clusters for calculations and of the storage?
9. The team has benefited from the fact that, at the national level, the reimbursement of the exome has been addressed (with a reimbursement level of 2205 EUR, the activities should be breakeven).

10. There is little mention of the activities of genetic counsellors (conseillers génétiques) in the presentations and reports. Could their role be presented more explicitly? What is their future role in clinical practice?
    The team clearly is looking at the future of clinical genetics (modification des pratiques), thereby dealing with issues like the diagnostic odyssey (l'impasse diagnostique) and secondary findings, and the role of rare disease reference centres. They have organised a workshop on the role of the clinical geneticists and genetic counsellors in the practice of medicine. However, it is not clear what the impact is of this initiative, the group seems to be hesitant to really propose a model.

11. Clearly, the pure research activities should be taken up/integrated into the classical research structures like INSERM. This is happening, but it would be good to evaluate the possibilities and make a plan. The SAB has the impression that there is a kind of urgency on this matter that has not been fully addressed.
12. For instance, therapies should become a research matter for the different CHUs.
13. In parallel, functional studies and mouse and other animal models should be developed by basic research teams. The SAB acknowledges that the number of researchers (PhD students) has increased. But to have a stable research basis, post-docs are important.

14. The plan for the integration of genomic testing into the clinical practice could be more ambitious. It was not clear to the SAB what the aims are, and it is not easy to find out what the ambitions of the centre are in relation to the national rare disease plan, and the national genomics initiatives. Obviously, the team is evaluating other sequencing platforms (like Sequel) but it is unclear where this fits in the team's strategy. At the technical level, significant efforts have been taken to evaluate the analytical and clinical performance of the NGS tests, and to reduce costs. Also, the ins-and-outs of variant interpretation and databases are being addressed.

15. Will the centre acquire sequencers to build the infrastructure locally?
    Will it be able to further invest in bio-informatics?
    Does the centre actively prepare for a next call of France Genomics (if one is to follow)?
    So the question is double, i.e. there are different levels of policy issues. For instance, how will the team link to the national initiatives (like e.g. Crefix). But also, how will it position itself in the 'sequencing landscape' in France. What would/could stop the team from sequencing elsewhere?

16. For the social science (sciences humaines et sociales, SHS) research within the project: it would be interesting to launch a transversal action, to measure the outcomes of the different projects using the same criteria.
    The different aspects of the introduction of genomics into health care have received significant attention. For instance, the groups have collaborated to develop the methodology and deliver the results of structural interviews with patients after the genetic consultation. This type of interactions are important.
    After 5 years of collaboration between SHS and biomedical scientists, it would be good to consider and develop projects that are more intrinsically linked to one another, or build upon one another. Currently, the SHS projects are very good, but they are largely 'exploratory'. So they do not necessarily address the very specific and concrete questions that may exist in society about genomics.
    Two projects are under construction: one on the diagnostic odyssey of patients (errance diagnostique) and one to address the needs and preferences of the citizens. It is good to not only address medical needs but also look at other societal obstacles. The SAB notes that it would be interesting to also investigate the 'non-responders', i.e. people who are reluctant to seek benefit from genomic medicine.
    The different groups should continue to invest in tools/skills for the study of the SHS aspects of genomics and genomic medicine. The SAB challenges the team to collaborate even more intensively and to go beyond the typical paradigms of SHS/biomedical research, and move from parallel to interdisciplinary research. The SAB also asks the team to further develop very targeted SHS (pre)projects, like for instance on upcoming issues like neonatal and prenatal genome sequencing.
    It is the way to maximally benefit from the multidisciplinary setting of TRANSLAD.

17. The team has impressed the SAB with the presentation on awareness, visibility and publicity (activités de sensibilité, lisibilité). The SAB congratulates the team on what has been realised with a limited budget: courses, information leaflets, videos, books, etc. This reflects a strong commitment of the team towards serving patients, parents and citizens.
    If possible, it would be interesting to know whether the impact has been/could be measured, e.g. how many people have actually participated to the activities, etc.
    Also, have these activities served a purpose beyond the provision of information: were the participants and patients solicited, were they asked about their opinions?
    To which extend were these activities embedded in the research of the team.

18. The team has offered support for the creation of patients/parents groups. There is a clear dynamic around this issue. The question is whether such groups have the

potential to become larger, i.e. to grow from regional initiatives to national associations. If not, they run the risk to further parcel out the landscape of family associations etc. in France. The team should decide whether 1. this is within the scope of the its activities, 2. whether money could be made available for such initiatives, and 3. what the best policy would be in view of the bigger picture of rare diseases activities in France.

19. The valorisation of the project has improved significantly since the previous visit. For instance, the team has been invited to join the SOLVE-RD project. This European projects gathers leading rare disease clinical and research centres, and the grant brings significant funding for the team. At the national level, there is the involvement in DEFIDIAG.
    The SAB congratulates the team with the overall added value that has been generated for TRANSLAD over the past 2 years.
    In this context, it would also be good to provide financial details about the projects that have been attracted, thanks to the TRANSLAD initiatives.