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How to cite

KAUR, Baljeet et al. Expert pathology for GTD : towards an international multidisciplinary team meeting (MDT). In: Gynecologic and obstetric investigation, 2024. doi: 10.1159/000536028

This publication URL: https://archive-ouverte.unige.ch/unige:174800
Publication DOI: 10.1159/000536028

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Gynecologic and Obstetric Investigation

Gynecol Obstet Invest , DOI: 10.1159/000536028
Received: August 18, 2023
Accepted: December 24, 2023
Published online: January 8, 2024

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ISSN: 0378-7346 (Print), eISSN: 1423-002X (Online)
https://www.karger.com/GOI
Gynecologic and Obstetric Investigation

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Expert pathology for GTD: towards an international multidisciplinary team meeting (MDT).

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Running title
International multidisciplinary team meeting (MDT) for GTD

Keywords
multidisciplinary team meeting**,** expert pathology, hydatidiform mole, trophoblastic tumour, survey

Word count (excluding abstract and references): 4736 words

Abstract

Background:
Gestational trophoblastic disease, comprising hydatidiform moles and gestational trophoblastic tumours, is extremely rare. Exact diagnosis is crucial to indicate the appropriate treatment and to prevent complications. The scarcity and variability in the number of cases available for reporting, lack of specialized training in GTD and non-existence of refresher courses available implies that the pathologist dealing with these rare and at times extremely challenging cases are not completely confident in their diagnosis.

Objectives:
To explore the benefits of implementation of an international multidisciplinary conference (virtual) to aid diagnosis of difficult cases and support clinical management of GTD.

Methods:
A short survey was circulated to all 46 members of the EOTTD pathology and genetics working party, and further spread to other colleagues who practice GTD. This showed that the pathologists and geneticists working with GTD patients do not feel adequately supported and equipped with dealing with these rare diseases.

Outcome:
Virtual cross-border MDTs were initiated in April 2022, bringing together participants from 11 European countries on a bi-yearly basis. Mean numbers of 3 patients are discussed during the MDTs followed by 3-4 QA cases. A participant survey was conducted at the end of virtual meeting with an average satisfaction rate of 9.5. The pathologists felt supported and benefited from networking and clinical collaboration.

Conclusions and Outlook:
This international multidisciplinary team meeting (MDT) continues to provide support in managing the uncertainty with difficult and rare cases and enhances the pathologists training and experience. The frequency of meetings

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and the number of cases discussed per meeting will be increased in 2023 given the positive response. This will empower individuals and organisations to work together and improve diagnosis and the prognosis for these young patients.

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Introduction

Moles, or molar pregnancies are the most common forms of gestational trophoblastic disease (GTD). Exact diagnosis is crucial to indicate the appropriate treatment and to prevent or at least be aware of the possible mid- and long-term complications giving rise to a gestational trophoblastic neoplasia. GTD is rare, with figures around 50 cases a year from a 4 million population [1]. With these numbers, getting experience in the histopathology of GTD is greatly hampered. Availability of "at home" medical treatment for first trimester miscarriage or non-evolving pregnancies further reduces the number of samples submitted for histopathological analysis [2]. Not surprisingly, a low throughput of pathological GTD diagnoses was reported [3]. Importantly, a significant fraction of partial moles were not clinically suspected, and they were diagnosed only after samples were sent for pathology analysis [4], highlighting the value of routine pathology analysis in the hands of experienced pathologists in the management of GTD. Furthermore, GTD diagnosis could be improved with the addition of ancillary techniques even among experienced pathologists with specialized training [5,6].

Sadly, specialized training in GTD is not included in most of pathology training programs, depending largely on the activity of the training unit and the interest of trainees. As mentioned earlier, the scarcity of cases poses difficulties in achieving proper training in most centers. Courses devoted to GTD training are not available. Therefore, attending pathologists would appreciate consultation availability, either at their own working center in the figure of a local expert or external consultation (local, regional, national, international) in order to deal with difficult or unusual cases.
In this report the reader will find the experiences of pathologists working with GTD in different settings, their training needs, the benefits that could be obtained from the implementation of a multidisciplinary conference or forum to facilitate discussion and advice on difficult or unusual GTD cases and develop a Quality Assessment initiative. A literature review encompassing the development of reference centers for trophoblastic diseases, the improvement in pathologic diagnosis through review in referral reference centers, and the benefits from international collaboration and biobanking is also provided.

Reference Centers for Trophoblastic Diseases

In North America, the John I. Brewer Trophoblastic Disease Center of Northwestern University Feinberg School of Medicine was set up in 1962 in Chicago. The objectives of the center were the study and treatment of gestational trophoblastic disease (GTD) [7]. Brewer was first to show that morbidity and mortality were reduced 9 times in patients with GTD treated by experienced physicians [8]. His findings were later confirmed in 2014, by a worldwide questionnaire survey [9].

This was preceded by the opening of the first GTD Reference Center in Brazil, in Rio de Janeiro, in 1959 [10]. GTD is 5 to 10 times more frequent in Brazil than in Europe and North America. Brazil, as fifth most populated and fifth largest country in the world, had to face major issues before the Brazilian Association of Gestational Trophoblastic Disease (BAGTD) could be launched in 2013. At the time of the report by Braga et al. in 2016, 38 centers were part of BAGTD. In order to overcome certain difficulties, a communication group via cell phone was set up among all GTD reference centers' directors, to discuss in real time the treatment options of unusual or serious cases. A training program was also implemented [10]. Development of Health Information Systems (HIS) further contributes to education and self-care [11].
Higher GTD frequencies have been reported from Asia, the Middle East, and Africa. Although GTD reference centers exist [12, 13, 14, 15] (South Korea, China, Senegal), the development of registries or opening of further reference centers may help with more accurate data collection. Recent reports from South Korea [16] and from the Chiba prefecture in Japan [17] document a similar molar pregnancy incidence as that in Europe or the USA. However, data retrieved from the Japanese GTD registration system, established in 1974, shows an average incidence of hydatidiform mole of 2.02 per 1,000 live births on average between 1974 and 2018, thereby confirming the higher incidence [18]. Interestingly, a decrease in the reported GTD cases to 1.02 in 2008 was followed by an increase reaching 1.69 GTDs in 2018. Indeed, prior to the third revision of the Japanese guidelines in 2011, the diagnosis of hydatidiform mole was made on macroscopy solely. The increase in the use of p57 immunohistochemistry was paralleled by an increase in the proportion of CHM from 2010 to 2018, from 37.3% to

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58.8%, although increased maternal age may also in part explain these numbers. This recent report is therefore a plea to the need for pathological assessment of these cases, and highlights the need for both diagnosis accuracy, and adequate data collection [18].
Other countries, such as Morocco, have implemented GTD management programs [19]. To achieve this goal, they developed standardized protocols, designed education and communication modules, and created a GTD electronic registry. They deplore the absence of referent pathologists in their program, which led them to opt for a one-year surveillance scheme for all patients, preferring enhanced patient security to the cost-effectiveness of histology-guided management.
In Europe, the first center for Trophoblastic Disease to be set up was the Charing Cross GTD Centre at Imperial College in 1972 and is now the world's largest GTD center. Two further GTD centers exist in the UK. The Sheffield Trophoblastic Disease Centre, established in 1973, is active in the North of England and North Wales. The Hydatidiform Mole Follow-Up Service, at Ninewells Hospital and Medical School, provides diagnosis and follow-up to women from Scotland having a hydatidiform molar pregnancy.
The Charing Cross GTD Centre served as an example to many centers in Europe. For instance, the French Trophoblastic Disease Reference Center was established in November 1999 in Lyon, following the London example, with the help of shared expertise. From that time on, the French center has been registering, monitoring and treating patients with GTD [20].
European countries have been progressively set up reference centers (Hungary in the mid-1970s, the Netherlands in 1977, Switzerland in 2009, Belgium in 2012, and Ireland in 2017). Support in the development of GTD centers has been provided by the European Organisation for Treatment of Trophoblastic Diseases (EOTTD), founded in 2010 [21]. The main aims were to improve the precision diagnosis and management of GTD.
The specialized care provided in GTD reference centers may also help patients deal with the emotional aspects and minimize psychological sequelae, in particular regarding evolution to a gestational trophoblastic neoplasm (GTN), or with regard to reproduction issues [22].

Referral to the Reference Centers for pathology reviews

Central pathology review is essential, and varying rates of diagnosis discordance between "expert" and "non-expert" pathologists have been reported. In a recent study from Belgium, Schoenen et al. [23] observed a 35% discordance rate. Whereas complete hydatidiform moles were correctly diagnosed by the initial pathologists in almost 95% of the cases, only 61% of the partial moles submitted for review were confirmed by the expert pathologists. The UK data also showed similar findings with a concordance rate of nearly 67% [24]. These numbers are similar to previous publications [25, 26]. Diagnosis was modified in 42% of the referred GTN, with tumor down-staging in 65%, and up-staging in 33% of the cases. These results highlight the need for expert central review of the cases.

Lower rates of discordance have been recently published in Switzerland, where the overall rate of agreement between the GTD reference center and the referring pathologists was 82% [27]. The hypothetical explanation provided was that most referring pathologists were residents in the hospitals that are part of the GTD reference center, and were therefore more likely to correctly identify GTD. This finding may support the importance of specific education in the optimal pathology and genetics diagnosis of GTD.

Cases are usually referred on a voluntary basis by the initial pathologist, or by the gynaecologist [23, 19, 27, 28] in most European countries (Belgium, France, Switzerland, The Netherlands). Patient informed consent is required. In the UK, all women diagnosed with GTD are registered and followed up at one of the three National reference centers. This is done mainly by the gynaecologists. The pathology material is reviewed for nearly all of these patients at the reference centres.

For pathology review, morphological evaluation of the initial slides is performed, and ancillary techniques performed when needed, thereby requiring one or more FFPE (formalin-fixed paraffin embedded) blocks. The realization of ancillary techniques (p57 immunohistochemistry, and genotyping) relies on the pathologist's opinion and expertise, as well as on availability.

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In an attempt to harmonize the diagnostic procedures, guidelines for pathological and genetic diagnosis of hydatidiform moles have recently been proposed by the Pathology and Genetics Working Party of the European Organisation for Treatment of Trophoblastic Diseases (EOTTD) [29]. The establishment of guidelines for the diagnosis of GTN is in progress.

Cross-border, multinational MDTs

Rare gynaecological tumours form the G2 domain of the European Reference Network (ERN) for rare or low prevalence complex diseases EURACAN (European reference network on rare adult cancers). Virtual clinical cross-border MDTs have been successfully initiated within EURACAN in November 2017, bringing together participants from 10 countries on a monthly basis. Mean numbers of 3 patients are discussed during the MDTs, some patients being discussed up to 6 times. A meeting summary with treatment recommendations is emitted after the MDT. Major benefits to patients were access to off-label treatments and inclusion into clinical trials in other countries. Health care professionals benefited from networking and clinical collaboration [30].

Biobanking

FFPE or frozen samples are usually archived in Pathology laboratories depending to local regulations and legislations. Nationwide data networks and archives, such as the PALGA network in the Netherlands [31], and more 'formal' biobanks exist. For instance, France has set up in November 2014 a national biobank of chorionic villi, decidua, and tumour samples from both patients with GTD, and control patients [32].
In the UK, the Charing Cross GTD Centre at Imperial College combines national and international databases together with their own tissue, urine and blood biobanks at the NIHR Imperial Biomedical Research Centre. Holding records of over 35,000 women, the Centre has the largest database of GTD patients in the world.

As in other rare diseases, the main aims of GTD biobanking is to encourage national and international collaborative research projects, allowing for better understanding of the pathophysiology of these diseases, the development of early diagnostic techniques, and the identification of therapeutic targets. Refining prognostic markers and improved patient risk stratification allows for targeted least toxic therapies.

Box 1 – Benefits of expert pathology review and MDT discussion to patients and Pathologists

⇨ Benefits to patients

- Rare diseases like GTD: centralized expert pathology and genetics review beneficial as only partial diagnostic agreement rates between "non-expert" and "expert" pathologists.
- Cross-border MDTs:
  - ❖ Reach a consensus diagnosis between experts in difficult cases.
  - ❖ Precision diagnosis and clinical management.

⇨ Benefits to health care professionals:

- ❖ Networking, collaboration, and diagnostic support.
- ❖ Provide education for general pathologists, and other "non-expert" pathologists.
- ❖ Provide continuing development and experience building for "expert" pathologists.
- ❖ Accumulative experience building for the team and re-enforcement.

The pathologists and geneticists' perspective

To understand how pathologists and geneticists working with GTD patients feel supported and adequately equipped with dealing with these rare diseases, we circulated a short survey. It was sent by email to all 46 members of the EOTTD pathology and genetics working party, and further spread to other colleagues who practice GTD.

A summary of results is shown is Figure 1 and the survey form can be found in supplementary files. Twenty-one pathologists and two geneticists responded, working in different settings, but the majority at university hospitals.

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Over half stated to have GTD central pathology review in their countries, what was expected given the participation of several colleagues from UK, France, Switzerland, and Sweden. This correlated with the case load per year and the number of pathologists reporting GTD. In countries with referring centers' there are smaller numbers of specialized pathologists reporting dozens to hundreds of cases per year. For instance, smaller countries such as Switzerland review approximately 50 cases per year [27], whereas in Belgium 179 cases were shared between 2 centres in 2020 [23]. In 2019, 1039 patients were registered in the French Trophoblastic Disease Reference Centre in Lyon (https://www.chu-lyon.fr/centre-de-reference-des-maladies-trophoblastiques). These numbers are shared by the world's largest GTD centre, the Charing Cross GTD Centre at Imperial College, who registers approximately 1200 patients a year (https://www.hmole-chorio.org.uk). On the other hand, outside that setting, GTD diagnosis is spread by a high number of pathologists who usually see less than 5 cases a year. Importantly the vast majority can consult with colleagues, and have access to ancillary techniques, mainly p57 immunohistochemistry, but frequently also ISH, flow cytometry and/or genotyping.

Many pathologists received some training in post-graduate years with GTD, ranging from 2 weeks to 6 months, but most emphasized that it was part of paediatric pathology training and not specific for GTD. Indeed, retrospectively collecting data available, we can assume that there is a shortage of specific training. Usually, GTD lectures are included as parts of more general courses in placental pathology such as in the Practical Placental Pathology: A "Hands-on" Gross and Microscopic Tutorial, Barcelona, January 2003 given by faculty members of the Massachusetts General Hospital, or in paediatric and perinatal pathology such as in the Advanced Courses on Paediatric and Perinatal Pathology held in a yearly basis under the auspices of the International Paediatric Pathology Association. However, the latter did not include gestational trophoblastic disease lectures in a regular basis until the 21st edition in 1999, and since then GTD lectures were included in the 26th, 30th, 34th, 36th, and the 39th edition, and in the 5th Update IPPA Course in 2022. Besides, attendance to these courses is restricted to perinatal and paediatric pathologists. GTD specific courses can be found occasionally as focused activities at congresses or scientific meetings such as the Diagnosis of Gestational Trophoblastic Diseases in the Molecular Era, Short Course at the 104th Annual Meeting of the USCAP, Boston, 2015.

During EOTTD working party meetings we discussed the possibility of making a forum for discussing difficult GTD cases, through multidisciplinary conferences (e.g., MDTs), including pathologists and geneticists. We also discussed the possibility of implementing quality assessment sessions. A small survey was sent to all working party members (supplementary file 1), through which we sought to know their needs about these topics. A summary of results and the survey form can be found in supplementary files (supplementary file 2). Globally, all 17 responders considered that such forum would be useful in their practice, either through email or live meetings. There was no agreement regarding the frequency of meetings, ranging from on demand, to 1 month or 2 months period. Given current diagnostic workload and schedule constraints, we later re-phrased this question reaching a consensus of a MDT every 4 to 6 months. A substantial number of pathologists stated to have whole slide imaging available to share and/or presented slides in MDTs. The vast majority was interested in participating in GTD QA sessions.

Based on this evidence, the EOTTD pathology and genetics party embarked on the journey to start virtual International MDTs to discuss rare or difficult GTD/ GTN cases. The working steps that were taken to achieve and complete the MDT process are listed in supplementary files (supplementary file 3). During 2022 the first two MDTs took place on April 27th and November 10th, both hosted by the Trophoblastic Tumour Screening & Treatment Centre at Charing Cross Hospital, in London. A call for cases was sent by email to all members of the working party. Anonymized clinical histories as well as digitized slides or histological pictures were shared by email prior to the meeting (supplementary file 4). In total, 5 cases (2 in the first meeting and 3 in the second), were presented by pathologists from different European countries (France, Portugal, Spain and Switzerland) (Figure 2). All cases were presented because of diagnostic difficulties whose differentials had clinical repercussions for the patients. These included differential diagnoses between GTD and non-GTD lesions, as well as differentials within different gestational trophoblast neoplasia. Each case presentation and discussion lasted 10 to 15 minutes, starting with clinical context, followed by digitized histological slides, to show morphological features, and results from ancillary and molecular techniques.
Cases were actively discussed by the different pathologists and geneticists present at the meeting, who shared their opinions, and a consensus was met for most cases. Attendance rates vary from 18 participants in the 1st MDT, to 25 participants in the 2nd MDT, from 11 European countries (Belgium, Denmark, France, Germany, Ireland,

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Norway, Portugal, Spain, Sweden, Switzerland, and United Kingdom) and French Guiana (Figure 3). In 2023, 6 cases were discussed, divided between the two meetings held during the first semester. During the second half of 2023, follow-up was provided for 3 patients, and an additional curettage specimen was discussed in one case. The meetings were hosted by different members of the group.

Relevant examples of the cases discussed during the MDTs included challenging tumors with choriocarcinoma features, with genotyping or other ancillary technique results allowing for classification as either gestational choriocarcinoma, or as somatic (endometrioid) carcinoma with choriocarcinomatous differentiation. Cases with morphological features of atypical placental site nodule (APSN) or of epithelioid trophoblastic tumor (ETT) were also discussed. Overlapping features in one case did not allow for a final definite consensus diagnosis, and patient follow-up with additional imaging was therefore recommended. Worrisome morphological features were discussed in a ruptured tubal pregnancy but felt to be insufficient for malignancy. Finally, a case of paternal uniparental disomy of chromosome 11 was considered as persistent GTD.

One challenging case presented at the meeting in November 2022 was a 25-year-old woman with history of anti-phospholipid syndrome secondary to SLE, under treatment with acenocumarol and hydroxychloroquine. She was diagnosed with an ectopic tubal pregnancy at 6.2 weeks of gestation. It was initially treated with methotrexate (95 mg). Two days later, she developed haemoperitoneum and a salpingectomy was performed. Pathology confirmed a ruptured ectopic pregnancy with haematosalpinx and blood clots consistent with haemoperitoneum. Histologically, the villi were small and uniform in size and showed increased stromal cell degeneration with karyorrhectic debris and apoptosis. However, no cisterns, trophoblastic pseudoinclusions or abnormal trophoblastic hyperplasia was seen. Immunocytochemistry showed a single focus of loss of (negative) p57 staining within stromal cells and cytotrophoblast with positive nuclear expression in the extravillous trophoblast. Most of the specimen otherwise showed retained expression of p57 (Figure 5). Cytotrophoblast was actively proliferating as shown by the expression of Ki-67. Genetic analysis of Short Tandem Repeats (STR) showed some maternal contamination but after the extraction of the maternal contribution all samples showed the same biparental diploid genotype, including those with divergent p57 expression. The question for the MDT was if this represented any kind of molar mosaicism.

The discussion within the group was that the morphological features in this case do not amount to a definite CHM, twin or mosaic pregnancy. The loss of p57 expression, in a single focus, although intriguing, showed no difference on STR genotyping to the background villi and demonstrated biparental diploid genotype.

One of the other members in the group had reported two similar cases where an early gestation, with no definite morphological features of a molar pregnancy (early CHM) showed complete absence of p57 expression. STR genotyping on both these cases were biparental diploid and no evidence of *NLRP7* or *KHDC3L* mutations were identified to suggest possibility of familial recurrent hydatidiform moles. Also, these patients did not present with history of recurrent moles. A case series from Johns Hopkins Medical Institutions (by Dr. Brigitte M. Ronnett) was quoted as evidence from literature, where among a series of 2329 products of conceptions, they identified 10 cases for which loss of p57 expression was inconsistent with genotyping results (none purely androgenetic). Out of these 10 cases, 5 were biparental and morphologically non-molar. Of these 5 cases, 1 non-molar specimen with loss of p57 expression was attributable to partial or complete loss of the maternal copy of chromosome 11 and 1 non-molar specimen showed Beckwith-Wiedemann syndrome. For 3 biparental non-molar specimens, genotyping did not identify a mechanism [33]. The case series suggested that this was likely due to other genetic alterations which are below the resolution of or not targeted by genotyping.

In view of the evidence from the literature, experience within the group of two similar cases and the members within the MDT agreeing that the overall appearances do not qualify as molar pregnancy in the case discussed, it was suggested that this is reported as non-molar. It was also advised that hCG levels should be followed up until it returns to normal and the follow-up provided at the next MDT, if possible. On follow-up, βHCG levels were normalized.

The important inference from the above case is that overdiagnosis of a nonmolar abortus with loss of p57 expression as a CHM would lead to unnecessary follow-up and restriction on pregnancy attempts for patients with infertility. Genotyping is valuable for addressing discordance between p57 expression and morphology but cannot elucidate certain mechanisms of lost p57 expression. Future studies and a collaboration between the international multidisciplinary team to collect more of such cases, especially from early gestation, could help in assessing mechanisms involved in 'switching-on' of p57 imprinting, in early gestation.

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In addition to case discussion, making use of the gathering opportunity at these MDTs, a quality assessment (QA) initiative was also started. In this setting, QA consisted of a brief proficiency test (5 questions), mainly with an educational purpose aiming to promote continuous learning. In the 1st MDT it focused on the assessment of typical molar disease diagnosis based on the examination of histology, p57 immunohistochemistry and genotypes (figure 4 A, B). The 2nd MDT QA focused on the interpretation of short tandem repeat (STR) / microsatellite profiles of gestational versus non-gestational lesions, determining causative pregnancy of a gestational tumour, and cut-offs for number of loci and peak size (figure 4 C, D).
In order to increase the understanding of the genetics in difficult cases, pathologists from the group suggested that a session on genetic profiling of GTD and selected gestational trophoblastic neoplasia be held by the geneticists. Continuing education will gradually be implemented during the MDTs.

Finally, at the end of the 2nd MDT a questionnaire about the quality of the meetings was performed. Average ratings (ranging from 1= very poor, to 10 =excellent) were as follows: 9.5 for case presentation, 9.5 for case discussion, 9.5 for QA cases, and 9.1 for QA discussion. Overall, participants were very satisfied with these MDTs, emphasizing its added value to their practice.

Discussion

GTD is a rare disease that originates from pregnancy. It is established and well reported in the literature that if treated in reference centres, it has high cure rates, even in cases of multi-metastatic neoplasia [34]. It is also recognised that precise pathological diagnosis is a critical component to management of this rare disease and an improvement in the quality of diagnosis is brought about by the central pathology reviews [26].
Findings of this study demonstrate that firstly, specialized training in GTD is not included in most of pathology training programs and this, supplemented by scarcity of cases, poses difficulties in achieving proper training. Second, there is no normal histology to compare with or serve as a benchmark when facing an uncommon pathological finding. In comparison to other body organs e.g., normal small/ large bowel, gallbladder, thyroid etc. a normal gravid uterus or a uterus post-partum showing how the trophoblast develops and involutes during and following pregnancy and the factors that affect these changes is not well understood and described. Last but the not the least, there is a wide variation in the number of cases seen by even expert gynae/perinatal pathologists with special interest in GTD. Continued professional development (CPD) courses specific to GTD training are not widely available. Therefore, many pathologists would appreciate consultation/second opinion either from a local expert or external consultation (local, regional, national or international) when confronted by these challenging cases.
Given the advancements in technology and availability of virtual platforms, digitisation of pathology slides or live sharing of cases via microscope cameras, it is now easier to enable networking and collaboration between pathologists in different countries. Cross-border virtual meetings provide unique opportunity to share difficult cases, at regular intervals, with clinical experts from different countries bringing in wealth of knowledge and years of clinical experience. This ensures thorough discussion and a consensus opinion, giving confidence to the signing pathologist supported by strength of numbers.
The advantages of live discussion include the opportunity to show areas of interest/difficulty by the signing pathologist followed by sharing of ideas and differential diagnosis and arriving at a collective diagnosis agreed by the team. However, as these meetings are conducted at fixed times, the urgent cases that arrive in the interim cannot benefit from team discussions. Also, a maximum of 2-3 cases can be discussed in depth to allow for time constraints and prevent decision fatigue. In addition, not all the pathologist in the forum can join at the particular time due to constraints at work, other commitments or when they are on leave.
These disadvantages could be overcome by an alternative method of sending the photomicrographs or PowerPoint presentation to the International GTD pathologist group. The individual pathologists could look at these in their preferred time and offer individual opinions. This can allow for real time discussion of urgent cases where opinions can be received within a time frame of 3-5 days. The disadvantage to this method is there is no real time sharing of ideas, team discussion and opportunity to learn from active discussion.
We therefore chose live discussions at regular interval as our preferred option of sharing cases with a provision to share any urgent cases on-line via e-mail if needed. During our trial phase of one year no cases were discussed via e-mail.

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Following the discussions, the ultimate responsibility of signing out the case lied with the original pathologist as they were in a position to discuss the consensus opinion and the differential diagnosis offered by the international faculty at their local clinical multidisciplinary team meetings/tumour boards and arrive at the final diagnosis in liaison with their clinical and radiology colleagues.

Our initial survey also highlighted the need for developing QA programme in trophoblast pathology as there is a wide variation in the number of cases seen by expert gynae/perinatal pathologists in different countries within the Europe. QA Programme in Pathology have known to improve patient safety and enhance patient care with timely, accurate and complete pathology diagnoses and reports. These are weaved into all systems of the laboratory, in most of the countries, and is dependent on a host of structural and personnel factors. Within our meetings we introduced this concept and there were 2-3 cases of pathology/genetics that were more straightforward. These were anonymised and a multiple-choice poll was set up for the participants to answer. A small educational component was attached to these cases to provide feedback and training on an ongoing basis.

We aim to keep a record of the cases discussed at the MDT and in QA setting to provide a reference resource (word file and pictures attached) and hopefully when we have a digital platform available, we would be able to store these anonymised cases with a feedback/follow-up as an educational resource for future reference.

Conclusions and Outlook

Following the initial two MDT's organised by Charing Cross Hospital (London), two further MDT/QA sessions have already taken place in 2023. These were hosted by centres from Denmark (2/03/23), France and Switzerland (15/06/23, 26/10/23). The increase in appetite for these MDTs/QA sessions is reflected by increased frequency in the current year (4 monthly), a greater number of pathologists/geneticists attending, and increasing number of cases discussed.

We hope that our combined endeavour to establish this international multidisciplinary team meeting (MDT) for trophoblast pathology would enhance the pathologists training and experience, provide continued professional development, and play an important role in managing the uncertainty with difficult and rare cases. Under the auspice of EOTTD we share the aspirations to improve patient safety and enhance patient care with timely, accurate and complete pathology diagnoses. This will improve pathology quality assurance and empower individuals and organisations, both at the GTD centre and smaller unit hospitals, to work together to make the ambition of improving the prognosis for these young patients a reality.

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Conflict of Interest Statement
The authors have no conflicts of interest to declare.
Funding
No funding was received for preparation of data for the manuscript.

Author contributions

BK: Drafted, revised the submitted the manuscript, designed the survey and chaired meeting discussions
AN: Drafted and revised the manuscript.
CB: Drafted and revised the manuscript, compiled results of surveys and prepared figures.
ALR: Drafted and revised the manuscript and reviewed the literature.

Acknowledgements
BK: acknowledges the support of NIHR Imperial BRC

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Figure Legends:
Figure 1 – Current status of GTD pathology in Europe: summary of survey results.

Figure 2 – The 2nd EOTTD pathology and genetics online MDT meeting, with live case presentation of digitized histological slides.

Figure 3 – Distribution of the 26 pathologists and geneticists that participated in the first two EOTTD international MDTs, representing 11 European countries and French Guinea.

Figure 4 - Quality assessment (QA) proficiency test: examples of pathology (A, B) and genetics (C, D) questions and corresponding summary of participants' answers.

Figure 5 - A. Focus of villi with increased stromal cell degeneration with karyorrhectic debris (H&E, original magnification 4x). B. Absent p57 expression in stromal cells and cytotrophoblast layer (original magnification 4x). C. Ki-67 expression shows evidence of proliferation (original magnification 4x). D. STR results in villous tissue for D8S1132 and D10S2325 markers. Blue dot lines indicate the amount of maternal contamination. Red parallel lines show the actual height of actual peaks. E. STR results from maternal tissue for D8S1132 and D10S2325 markers

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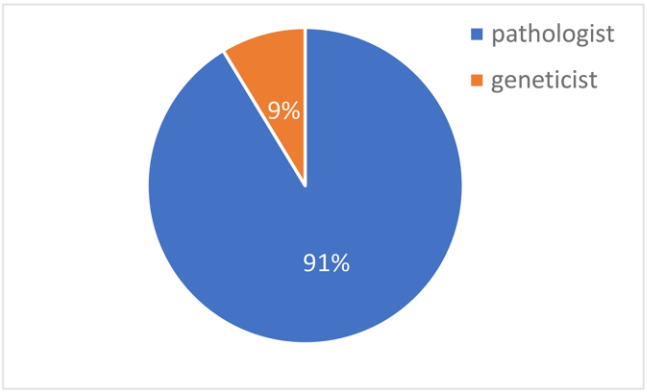
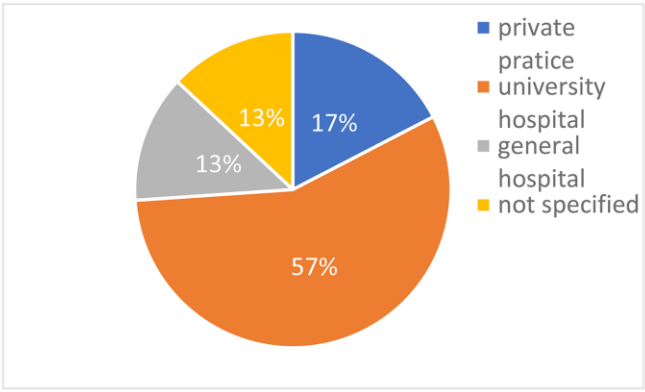
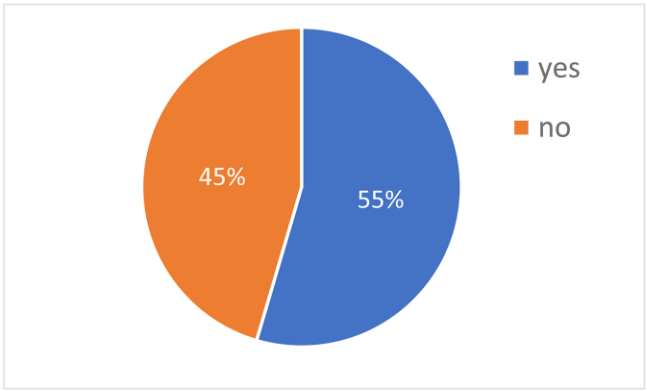
What is your speciality?



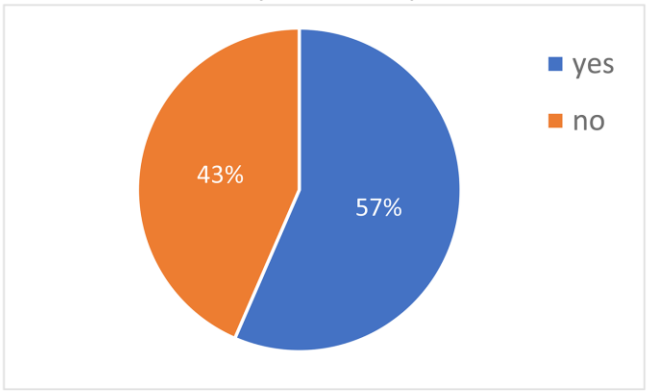
What is your type of practice?



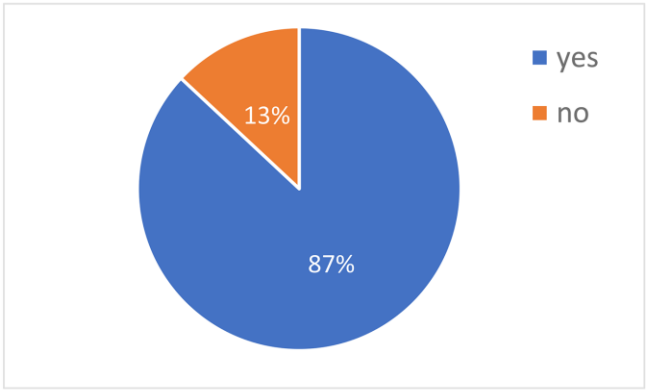
Did you receive training in GTD?

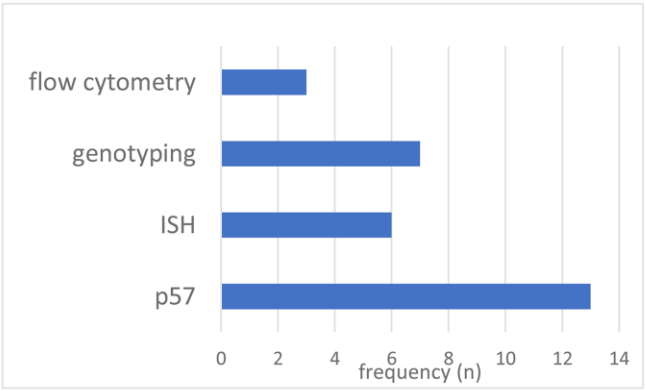


Do you have central pathology review in your country?

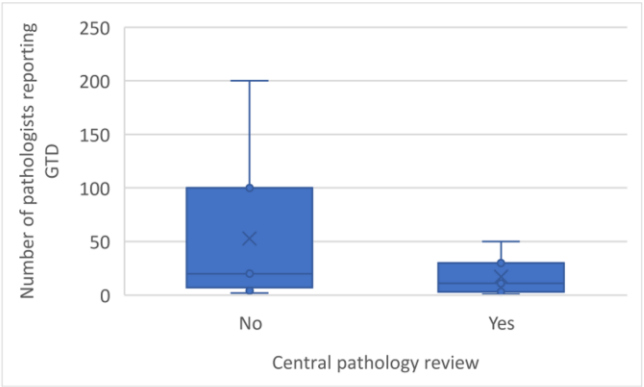


Do you have an easy access to ancillary & molecular techniques? Which?

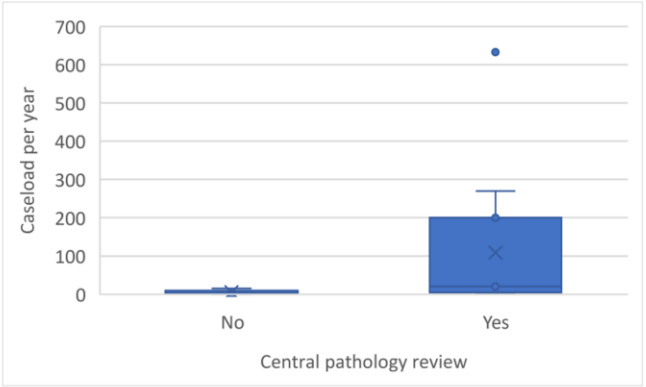




How many pathologists are there in your country reporting GTD?



What is your caseload per year for GTD?



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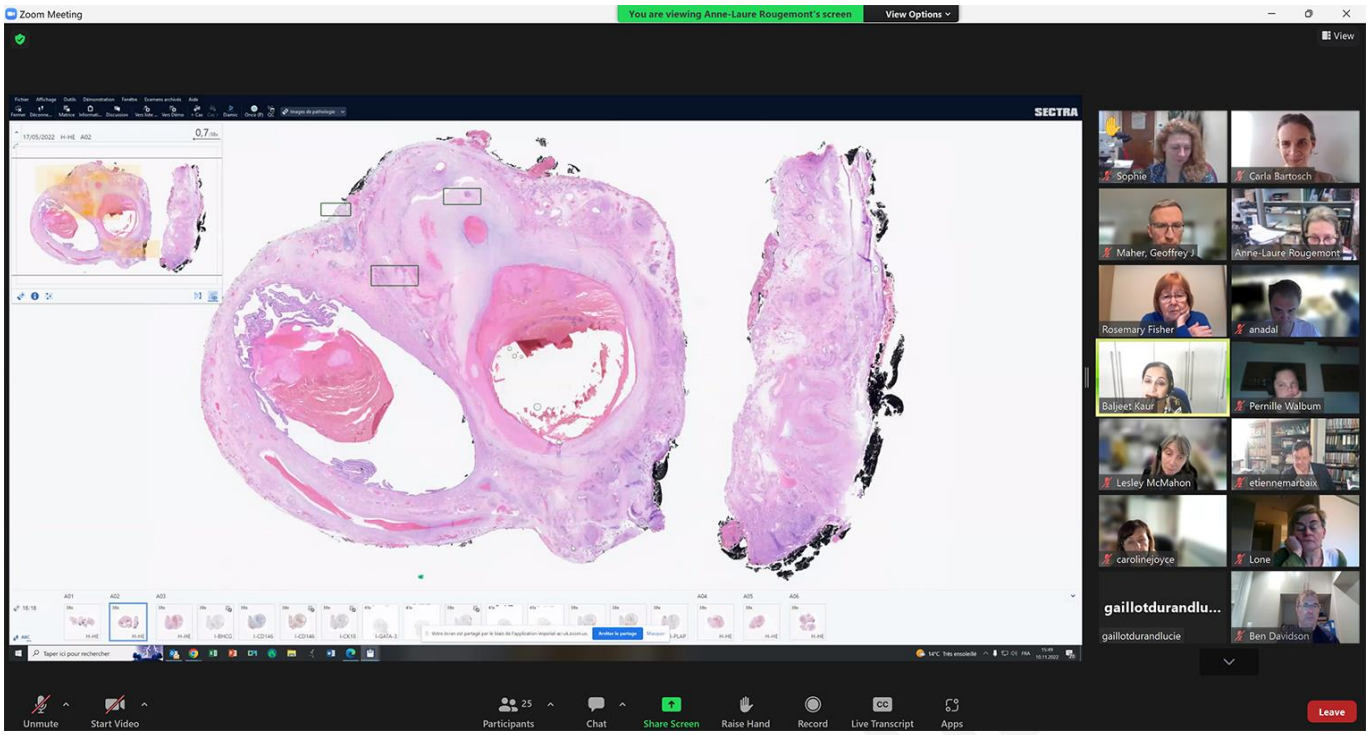

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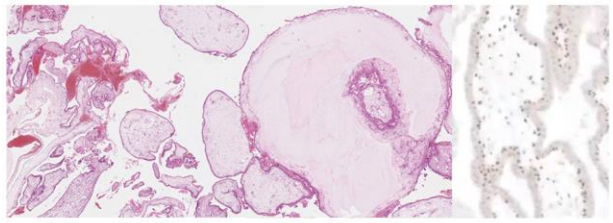

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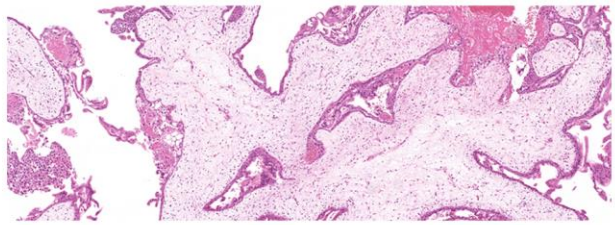

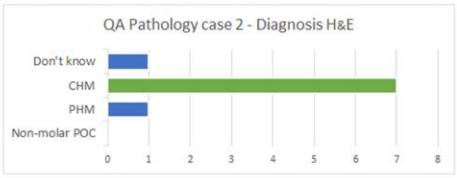

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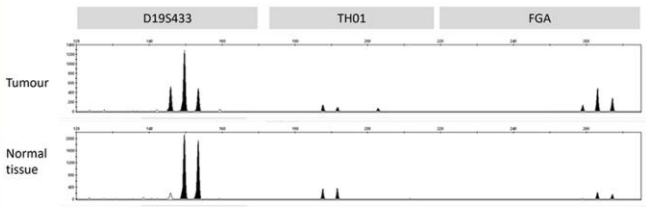

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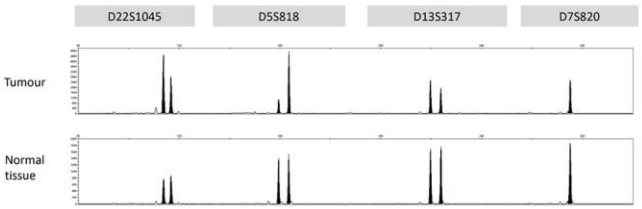

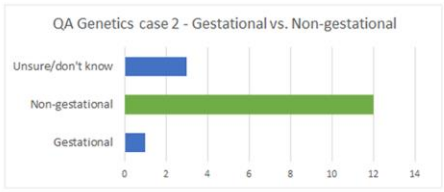

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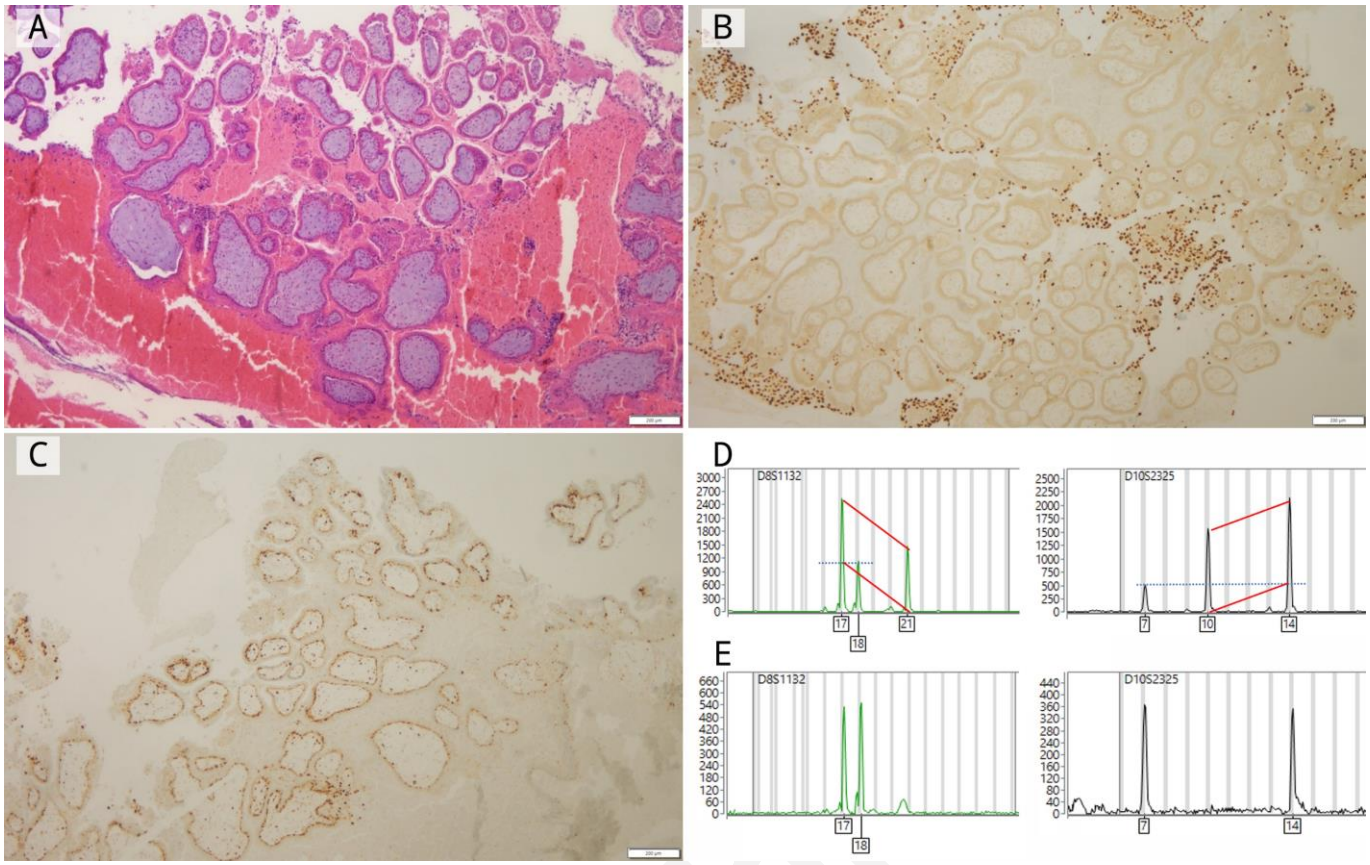

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