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Utility of a mainstreamed genetic testing pathway in breast and ovarian cancer patients during the COVID-19 pandemic

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\textbf{A R T I C L E  I N F O}

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\textbf{A B S T R A C T}

\textbf{Introduction:} Mainstreamed genetic testing (MGT) obviates the need for a cancer genetics consultation, since trained oncologists (O) and gynaecologists (G) provide counseling, prescribe testing and deliver results. We report results from our MGT program and emphasize its utility during the COVID-19 lockdown, when cancer genetics clinics had suspended their activity.

\textbf{Methods:} An MGT pathway for breast and ovarian cancer (BC/OC) patients was established in Jan-2018 between the Assistance Publique - Hôpitaux de Paris.Sorbonne Université Cancer Genetics team and the Oncology/Gynecology departments at one teaching and two regional hospitals. Trained O+G evaluated patients with the Manchester Scoring System. A 12-point threshold was recommended for testing. Next-generation sequencing of BRCA1, BRCA2, PALB2, RAD51C and RAD51D was performed. Results were delivered to the patient by O/G. Pathogenic variants (PV) carriers were referred to the genetics clinic. Results are reported for the 2nd-Jan-2018 to 1st-June-2020 period. That includes the eight-week COVID-19 lockdown and three-week de-confinement phase 1.

\textbf{Results:} Results were available for 231/234 patients. Twenty-eight (12.1\%) carried a PV. Of the 27 patients tested during the COVID-19 period, three carried a PV, two in BRCA1 and one in RAD51C. The clinical impact was immediate for the two BRCA1 BC cases undergoing neo-adjuvant chemotherapy, since double mastectomy and salpingo-oophorectomy will now be performed using two-step strategies.

\textbf{Conclusions:} MGT guaranteed care continuity in BC/OC patients during the critical phases of the COVID-19 pandemic, with immediate implications for PV carriers. More broadly, we report for the first time the successful implementation of MGT in France.

\begin{itemize}
\item 1. Introduction
\end{itemize}

On March 16, 2020, as the exponential increase in COVID-19 cases was threatening to overwhelm the French health care system, the country went into lockdown. People were not allowed outdoors but for very specific reasons, and working from home became normal for most individuals. Non-urgent medical care, including clinical cancer genetics, was suspended or drastically reduced in order to minimize patients’ and
medical professionals’ exposure to the virus.

Mainstreamed genetic testing (MGT) obviates the need for a cancer genetics consultation for most eligible cancer patients, since trained oncologists (O) and gynecologists (G) provide genetic counseling, prescribe germline testing and deliver results (Rahman et al., 2019). Only complex cases and pathogenic variant (PV) carriers are referred to the cancer genetics team. It was only proposed recently as an alternative to traditional cancer genetics clinics-based pathways (George et al., 2016).

Following reports from the United Kingdom of favorable outcomes in ovarian cancer (OC) patients (George et al., 2016), we implemented MGT in breast and ovarian cancer (BC/OC) patients for the first time in France at one teaching and two regional hospitals in the Paris region. We report herein our results and show how it guaranteed continuity of care during the COVID-19 lockdown and de-confinement phase 1.

Fig. 1. Mainstreamed genetic testing pathway for breast and ovarian cancer patients. MDT: multidisciplinary team, VUS: variant of unknown significance.
2. Methods

An MGT pathway for BC/OC patients was established in January 2018 between the Assistance Publique - Hopitaux de Paris (AP-HP), Sorbonne Université Cancer Genetics team and the Oncology and Gynecology departments at Tenon University Hospital (Paris), Centre Hospitalier Sud Francilien regional hospital, and Groupe Hospitalier de l’Est Francilien regional hospital. Its aims were to improve access to testing in patients from the Ile-de-France region living far from Paris-based genetics clinics, and to bypass increasing consultation waiting times. Approval was obtained from the Institut Universitaire de Cancérologie - Sorbonne Université scientific committee.

O + G participated on a voluntary basis, as traditional referral pathways remained available. They received a 20-min custom-made e-learning audio slideshow summarizing the principles of BC/OC genetic susceptibility, patient selection, informed consent, germline testing, carrier management, and cascade testing in relatives of positive cases (Fig. 1). First-line referral of complex cases to cancer genetics, e.g., those suggestive of the rare Li-Fraumeni syndrome, was strongly encouraged. If a cancer susceptibility PV had already been identified in the family, patients were excluded. BC/OC patients were evaluated using an excel version of the latest Manchester Scoring System, with minor modifications (supplementary table 1) (Evans et al., 2017). A 12-point threshold was recommended for testing, which corresponds to a 6–10% PV detection rate in the BRCA1-BRCA2 major BC/OC susceptibility genes in a British population (Evans et al., 2017; Flamm et al., 2020). O/G provided basic genetic counseling and prescribed testing at or shortly after cancer diagnosis. Patients were given an one-page document summarizing the information given during a traditional cancer genetics consultation. On February 4th, 2020, an educational video created with the Gynecology team and the Oncology and Genetics team was available online to patients (https://www.youtube.com/watch?v=5YzfB0w8xel1). Blood was drawn immediately afterwards. O/G could contact the cancer genetics team at any stage of the process.

Although the MGT program was developed for BC/OC patients, testing prescription was tolerated in patients with other cancers when the context was suggestive of BRCA1-2/PALB2/RAD51C-D-associated susceptibility.

A single academic laboratory centralized testing, using a next generation sequencing panel including the BRCA1, BRCA2, PALB2, RAD51C and RAD51D genes. Results were delivered to the patient by O/G, or at the O/Gs’ request, by the cancer geneticist. All PV carriers had to be referred to the cancer genetics clinic. Multidisciplinary team discussion of cases for whom no PV was identified was encouraged. Variants of unknown significance were discussed on a case by case basis.

Results are reported for the January 2, 2018 to June 1, 2020 period. That includes the eight-week COVID-19 lockdown (16th March – May 11, 2020) and the following three weeks (de-confinement phase 1) when travelling restrictions were still present, hospital activity had not returned to normal, and most patients were reluctant to attend non-essential consultations.

3. Results

A total of 234 patients had MGT (Table 1), 223 women and 11 men. Of those, 27 had testing during the COVID-19 period. Mean age at cancer diagnosis was 52 (range 22–90). Among women, 166 had BC, 52 OC, two BC and OC, one pancreatic cancer and one endometrial cancer with a BC family history. Diagnosis was missing for one patient. All men had BC.

As of August 25, 2020, results were available for 231/234 patients. Of those, 195 had their results delivered by the O/G and 24 by the cancer genetics team. Eight patients are yet to attend their medical appointment and four died shortly after genetic testing. Median turnaround time for testing was 70 days, similar to the turnaround time in the traditional pathway (68 days).

| Table 1 | Patients who had mainstreamed genetic testing since program inception, and specifically during the COVID-19 lockdown and de-confinement phase 1. Next generation sequencing of the BRCA1, BRCA2, PALB2, RAD51C, and RAD51D genes was performed. |
|---------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Tested  | Results available (N) | PV identified (N) | PV detection rate |
| Overall | Jan 2, 2018–Jun 1, 2020 | 234 | 231 | 28 | 12.1% |
| Female breast cancer | | 166 | 165 | 19 | 11.5% |
| Ovarian cancer | | 52 | 50 | 5 | 10% |
| Breast and ovarian cancer | | 2 | 2 | 0 | 0% |
| Male breast cancer | | 11 | 11 | 3 | 27.3% |
| Other | | 3 | 3 | 1 | 33.3% |
| COVID-19 period | Mar 11, 2020–Jun 1, 2020 | 27 | 25 | 3 | 12% |
| Breast cancer | | 18 | 17 | 2 | 11.8% |
| Ovarian cancer | | 7 | 6 | 1 | 16.7% |
| Breast and ovarian cancer | | 1 | 1 | 0 | 0% |
| Other | | 1 | 1 | 0 | 0% |

PV: pathogenic variant.

a as of August 25, 2020.

b Female only, no male patients with breast cancer had genetic testing during the COVID-19 period.

Twenty-eight patients (12.1%) carried a PV in BRCA1, BRCA2, PALB2, RAD51C or RAD51D (Table 1). All but three carriers who had their results delivered by the O/G were referred to the cancer genetics clinic. Two are yet to accept and one died.

Of the 27 patients tested during the COVID-19 period, three carried a PV, two in BRCA1 and one in RAD51C. The two BRCA1 PV carriers were female patients aged 40 (patient 1) and 54 (patient 2) with triple-negative ductal breast cancer, bilateral and unilateral respectively. Both were undergoing neoadjuvant chemotherapy at the time of writing. Given the genetic results, patient 1 will now have bilateral mastectomy instead of the initially-planned double lumpectomy. Risk-reducing salpingo-oophorectomy will be scheduled afterwards. As for patient 2, lumpectomy will be performed, but in association with reduction mammoplasty and risk-reducing salpingo-oophorectomy. Double mastectomy will follow in the subsequent months. Regarding the RAD51C PV carrier, debulking surgery has just been performed after three cycles of chemotherapy.

4. Discussion

Monahan et al. recently predicted that the suspension of screening colonoscopies in Lynch syndrome patients during the COVID-19 pandemic, and their only slow resumption afterwards, would result in an excess of advanced-stage colorectal cancer diagnoses (Monahan et al., 2020). In the English population as a whole, substantial increases in the number of avoidable cancer deaths in England are predicted as a result of diagnostic delays (Maringe et al., 2020). As for genetic susceptibility to BC/OC, we expect that the unavailability of genetic testing will lead to suboptimal cancer treatment and risk management in patients carrying PV, and as a result in avoidable deaths in the long term.

Genetic testing in cancer patients was until very recently exclusively provided by clinical cancer genetics services. With MGT, testing is integrated into oncology care. It was first introduced in the United Kingdom in OC patients in the mid-2010s (George et al., 2016; Rahman et al., 2019). MGT seemed the only way to guarantee testing in all women with high-grade OC, as recommended by national guidelines following the development of PARP-inhibitors. MGT was subsequently expanded to BC, and proved to be highly acceptable to both patients and
O/G (Kemp et al., 2019).

The French AP-HP Sorbonne Université MGT program was launched in January 2018. On March 16, 2020, the first lockdown day, 207 patients had already been included. Our paper shows how MGT guaranteed continuity of care during the COVID-19 pandemic, as BC/OC patients were still prescribed genetic testing while genetics clinics had discontinued their activity. Among the 27 patients tested between 16th March and June 1, 2020, three carried a PV in a cancer susceptibility gene. The clinical impact was immediate for two BRCA1-positive BC cases, since double mastectomy and risk-reducing salpingo-oophorectomy will now be performed using two-step strategies. With the looming threat of re-confinement due to the rising number of new COVID-19 cases in France and in neighboring countries, functioning MGT pathways such as ours are more needed than ever.

More generally, we have shown for the first time that MGT could be successfully implemented in France, a country with a more conservative attitude to genetic testing compared to the UK or US. It allowed for the rapid testing of 234 patients at their point of care. O/G were comfortable using a computerized version of the Manchester Scoring System for patient selection. The 12.1% PV detection rate at the 12-point threshold was comparable to rates observed in more traditional settings in France, but slightly higher than rates reported in British patients (Evans et al., 2017; Flaum et al., 2020). This warrants further exploration.

Finally, all but two eligible PV carriers have attended the recommended cancer genetics consultation. Flaum et al. also reported that a small minority (2/39) of PV carriers identified via MGT pathways in Northwestern England declined their cancer genetics appointment (Flaum et al., 2020). Nevertheless, long-term risk management and the importance of cascade testing in relatives have been addressed by an expert team in the vast majority of cases from our series, and we are hopeful that in the end the two remaining patients will understand the importance of a referral to our cancer genetics clinic.

Author contributions

Study concept and design: Benusiglio, Ezenfis, Byrde, Chabbert-Buffet, Gligorov, Coulet.

Acquisition, analysis, or interpretation of data: all author.

Drafting of the manuscript: Benusiglio.

Critical revision of the manuscript for important intellectual content: all authors.

Declaration of competing interest

Benusiglio: Astra Zeneca (honoraria), Roche (honoraria), Geneticancer (patient association, scientific committee member).

Chabbert-Buffet: Geneticancer (patient association, scientific committee director).

Gligorov: Roche Genentech, Novartis, Onxeo, Dachii Sankyo, MSD, Isai, Genomic Health, Ipsen, Macrogenics, Pfizer, Mylan, Lilly, Immunomedics, Sandoz. Honoraria or symposium/travel funding.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmg.2020.104098.

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