BEAUTY AND BEAST:
INTEGRATING MULTIPLEX PANELS INTO HEREDITARY CANCER GENETIC COUNSELING*

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Next generation sequencing technology (NGS) is revolutionizing the clinical genetic testing arena and subsequently driving broad and significant changes to clinical service provision. Utilization of this new generation of technology has resulted in a dramatic decrease in the cost of genetic sequencing, from roughly $10 million (USA) for a human genome in 2001, to under $10,000 as of 2014 (WETTERSTRAND, 2014). Commercial genetic testing laboratories have responded with the rapid establishment of multiplex gene panels for assorted indications including cardiomyopathy, intellectual disability and cancer. For each indication there is an ever-increasing array of options for clinicians and patients to consider. Promises and advantages of panels include increased efficiency and diagnostic certainty for both clinicians and patients, while concerns include increased uncertainty and unclear clinical utility (MAUER, 2013; DOMCHEK, 2013). In order to effectively incorporate panel testing into practice, genetic counselors and other health care practitioners need to know when to choose multiplex testing, how to select a panel, and how best to present the options to patients to facilitate informed decision-making and consent. Finally, appropriate clinical management recommendations should be made based on multiplex panel results. Best practice guidelines and new models of care are needed to ensure optimal
and consistent patient care. This paper provides a general overview and evidence informed opinion regarding the current status of panel testing in the field of hereditary cancer genetic counseling.

HEREDITARY CANCER GENETIC COUNSELING

The birth of the profession of genetic counseling was a direct result of technological advances in genetics, namely amniocentesis and karyotype analysis. Established in 1969, the Masters degree program at Sarah Lawrence College addressed the gap between the emerging use of genetic technologies in healthcare and lack of patient and health care practitioner’s understanding of genetics. This was also a time of social and political change, including a shift in medical decision making from a paternalistic model to one driven by patient choice (STERN, 2009). The goals of genetic counseling are to provide effective counseling and education in order to facilitate informed decision making (BIESECKER, 2001). With this foundation, genetic counseling practice has continued to evolve in response to technological advances and the inherent uncertainty of test results including prenatal serum screening, chromosome microarray, non-invasive prenatal testing. Genetic counseling is now charged with integrating NGS and multiplex testing into appropriate clinical care.

Hereditary cancer genetic counseling is well suited to the clinical application of multiplex gene panels due to heterogeneous phenotypes and the growing list of cancer susceptibility genes. Up to 10% of all cancer types are estimated to be due to a hereditary susceptibility (GARBER, 2005; CHEN, 2006). Following the identification of the BRCA1 and BRCA2 genes in 1994/1995, genetic counseling for hereditary cancer became broadly incorporated into North American healthcare (MIKI, 1994; WOOSTER, 1995); approximately 30% of the roughly 3000 genetic counselors in North America specialize in cancer genetics (NSGC, 2014). Published practice standards for cancer genetic counseling include criteria for when individual gene tests should be offered, and what should constitute cancer risk assessment and counseling. These guidelines recommend reviewing syndrome-specific information on risks and clinical management options with patients as part of informed choice for cancer genetic testing. Most practice guidelines highlight clinical utility as a central tenet to cancer risk assessment and genetic testing (ROBSON, 2010; NICE, 2013; NSGC, 2014). These practice guidelines were developed prior to the availability of multiplex cancer panels, and significant revisions are needed in order to incorporate multiplex testing.

INCORPORATING MULTIPLEX PANELS INTO CLINICAL PRACTICE

The first multiplex cancer gene panel was launched in February 2012 and included a combination of 14 high and moderate risk breast cancer susceptibility genes exclusive of BRCA1/2. Since then, the pace of incorporation of multiplex cancer panels into routine clinical care has been rapid. A survey of North American genetic counselors in November 2012 found 30% of respondents had never ordered a panel, with limited professional knowledge cited as a major contributing factor (LUNDY, 2014). A second
survey in the fall of 2013 identified only 13-17% of respondents had direct experience ordering a breast or colon panel, respectively and again identified low general knowledge scores as a contributing factor (MCKENNA, 2014). By March 2014, survey results indicated 94% had discussed panel based testing for hereditary cancer assessment and 80% had direct experience ordering a panel (YOUNG, unpublished data). Significant differences in experience are apparent between the United States and Canada, with 89% and 23% of counselors reporting utilization of panels respectively (YOUNG, unpublished data). For those not offering panels in both countries, 90% indicated they would like the option of incorporating multiplex testing into clinical practice, but were limited by lack of institutional protocols and/or guidelines.

This rapid incorporation of panels in the absence of guidelines is changing both the approach and consistency of care in cancer genetic counseling. Surveys of cancer genetic counselors in 2013/14 about the experiences and impact of multiplex testing in clinical care identified that 93% of genetic counselors have changed the type of genetic tests being ordered and 99% reported a change in counseling practice. Specific changes included ordering multiplex panels and the need to modify counseling strategies to facilitate patient decision-making. The most significant events for these changes were the availability of multiplex panels (45%) and the AMP vs Myriad decision in June of 2013 (44%) that opened the door for any lab to incorporate BRCA1/2 into their platforms (HOOKER, 2014; YOUNG, unpublished data).

The impact on consistency in practice between genetic counselors is also quite dramatic. When a group of experienced cancer genetic counselors were presented with pedigrees suspicious for hereditary breast cancer and asked to select first line and reflex testing preferences, the impact of multiplex panels on test selection practices identified significant inconsistency between practitioners. In the absence of a panel, over 90% of genetic counselors opted for BRCA1/2 testing, and if results were normal 80% opted for no further testing. With multiplex panels on the menu, only 50% opted for BRCA1/2 as the first tier test, and 60% reflexed to additional panel testing following normal BRCA1/2 results (HOOKER, 2014).

Recent National Comprehensive Cancer Network (NCCN) guidelines recommend NGS be offered by trained genetic health providers as a second tier test for high-risk cancer patients (NCCN, 2014). The BRCA1/2 genes explain 50-85% of mutation positive hereditary breast and ovarian cancer families, (HBOC), and remain the most likely candidates on the breast testing menu (CHONG, 2014). However one study identified over 30% of genetic counselors opted to start with a breast multiplex panel including BRCA1/2, and another 10% opted to start with a general cancer panel including BRCA1/2 for patients with personal and/or family histories suspicious for hereditary breast cancer (HOOKER, 2014). An investigation into the clinical circumstances that influenced a genetic counselor’s decision to pursue panel testing as a first tier test found complexity of family history to be a significant factor. When the pedigree was suggestive or more than one syndrome, 74% of genetic counselors would start genetic testing with a panel (MCKENNA, 2014). When BRCA1/2 were selected as the first tier test for HBOC and results were normal, family history continued to significantly impact the choice to utilize multiplex panels as a second tier test. Panels were selected by only 9.8% of
counselors when the family was much less suspicious of a high risk hereditary cancer gene (e.g. the patient and one family member were diagnosed with breast cancer over age 50), but were opted for by 72% of genetic counselors when the family history was strongly suspicious of a hereditary predisposition (e.g. the patient was diagnosed with breast cancer under age 45 and multiple family members were diagnosed under age 50) (LUNDY, 2014).

While recommendations to offer genetic testing continues to be based on clinical presentation, genetic counselors’ choice of first tier or second tier test is impacted by non-clinical factors, not the least of which are cost implications. More than 22% of genetic counselors cited insurance pre-authorization and a further 20% identified out of pocket costs to patients as major factors for choosing multiplex panels as a first tier test and foregoing single gene testing (YOUNG, unpublished data). In reality, if their patients have one option for genetic testing costs to be covered, then panel testing will take precedence over single gene tests regardless of clinical presentation. Thus, cost implications may be responsible for some of the variability in genetic counselor practice.

Once the decision to use a panel is made, there are many factors to consider in the selection process. The number of genes per panel varies from 4 - 61, with costs ranging for $1500 to $4500 (USA) dollars. Cost is an obvious factor relevant to all payers, whether covered by the patient, a for-profit private insurance company, or a publically funded non-profit insurance system. While absolute cost differences are easy to compare, they may not reflect the inherent value of the results. The issue of test turn-around-time (TAT) may also be relevant due to implications for surgical decision-making. However recent announcements of results available in 7-14 days may mitigate this issue (AMBRY, 2014). While factors of cost and TAT are relatively easy to compare, the complexity involved in determining panel composition and understanding differences between laboratory testing strategy requires educated genetic practitioners to guide the process.

**PANEL COMPOSITION AND THE IMPACT ON GENOTYPE-PHENOTYPE CORRELATION**

Panels may be targeted to specific tumour types such as breast or colon cancer, or may be comprehensive and inclusive of genes associated with multiple tumour types. Proponents of both targeted and comprehensive multiplex panels cite the value of increased diagnostic certainty in a shorter time interval compared to an iterative approach. Mutation detection rates are increased by 7-15% over single-gene analysis, depending on the composition of the panel (MAUER, 2013; CHONG, 2014; LADUCA, 2014). But more genes on a panel and higher mutation detection rates do not necessarily equal a better test, unless you understand what the genes do.

Targeted panels are helping to expand our understanding of gene prevalence and penetrance for specific tumour types. For example, patients with significant personal and/or family history of breast cancer are now being identified with *ATM, CHEK2, PALB2,* and *RAD51C* mutations; genes not routinely assessed prior to multiplex panels due to the costs of iterative testing (ROSENTHAL, 2014; LINCOLN, 2014; KURIAN, 2014). Now that multiplex panels have improved the cost effectiveness of testing these genes,
penetrance information is likely to change. For example the RAD51C and RAD51D genes are known breast and ovarian cancer susceptibility genes with low prevalence. While these 2 genes were previously reported to confer an increased risk for breast cancer, mutations in them had not been reported in multiple studies of breast cancer only families with sample sizes up to 1053 (THOMPSON, 2012). When these genes were analyzed on a much larger high-risk cohort of 10,000 patients through multiplex panel testing, mutation prevalence was indeed small at 0.4%, however 30% of the RAD51C/D mutations were found in breast cancer only families (STUENKEL, 2014).

Results from comprehensive panels are broadening our perspective of genotype-phenotype correlation; Walsh et al. identified two MSH6 mutation carriers who had no family history of Lynch syndrome in a group of incident ovarian cancers, and Kaushik et al. found MSH6 mutations in breast cancer families with no history of colon or ovarian cancer. So which is superior, targeted or comprehensive testing? Both have limitations worth consideration before deciding. Targeted cancer panels may miss identifying mutations of clinical relevance for genes not traditionally associated with the patient’s presentation (KAUSHIK, 2014). With comprehensive panels, there is a greater chance of indentifying pathogenic variants but also variants of uncertain significance (VUS) in genes that appear to be unrelated to the clinical presentation. Interpreting the results and recommending clinical follow-up in these cases raises complex issues (RAINVILLE, 2014).

Both targeted and comprehensive panels may be comprised of high, moderate and/or low penetrance genes. A survey of cancer genetic counselors in early 2014 indicated that 60% preferred targeted panels, 30% preferred comprehensive panels containing only highly penetrant genes; while less than 10% would choose a comprehensive panel with high, moderate and low penetrance genes (YOUNG, unpublished data). Concerns raised against panels comprised of moderate and low penetrance genes include limited clinical utility of results particularly for genes on the panel with limited screening guidelines (LUNDY, 2014). This trend indicates genetic counselors have a preference for panels with lower chances of uncertain results and a higher degree of clinical utility which is consistent with published guidelines.

Major commercial laboratories provide intriguing outcomes data worthy of consideration. Myriad Genetic Laboratories conducted a retrospective analysis of 15,263 patients tested for a 25 gene comprehensive panel from Sept 2013-June 2014. The overall mutation detection rate was 8.2%, with just less than 1% of patients having a mutation in more than one gene. For those with a mutation, 70% met NCCN criteria for HBOC, 7.5% met NCCN criteria for Lynch syndrome, 19% met both HBOC and Lynch criteria, and roughly 3% met no criteria. Of particular interest is the patients who met criteria for testing for one syndrome yet were found to have a mutation in a gene for a different syndrome. In 1-2% of patients who met NCCN criteria for HBOC, mutations were identified in genes not clearly associated with breast or ovarian cancer, including MUTYH, APC, CDKN2A, and SMAD4.

A further 5% of mutations were found in Lynch syndrome genes. For patients who met NCCN criteria for Lynch syndrome, 16% had mutations in genes not associated with colon, endometrial, ovarian or gastric cancer and 6.5% had mutations in BRCA1/2 (KAUSHIK, 2014). These results pose difficulty in assigning lifetime penetrance risks and
for recommending appropriate clinical management strategies. Current penetrance and risk estimates may not be appropriate when applied to families ascertained differently and in the absence of supportive family history. Without known risks, determining the risk-benefit ratio of management options is impossible. For example, when a \textit{CDH1} mutation is identified in a breast cancer patient with no personal or family history of gastric cancer, is it appropriate to recommend prophylactic gastrectomy, or to consider routine endoscopy with its unproven diagnostic value (KURIAN, 2014)?

The challenge of clinical follow-up is even greater for moderate and low penetrance genes. One study of 708 HBOC patients reported a 15\% mutation detection rate using a 16 gene panel; of these 59\% were in \textit{BRCA1/2}, 1\% in \textit{TP53} and 31\% in other genes with less substantial clinical utility including \textit{PALB2}, \textit{RAD51C}, \textit{CHEK2}, \textit{ATM}, \textit{NBS1}, \textit{MLH3}, \textit{MRE11A}, and \textit{RAD50} (CASTÉRA, 2014). Another group reported an 11.4\% mutation detection rate from a panel of 40 putative cancer genes tested in 141 women who previously tested negative for \textit{BRCA1/2}. The additional genes were selected based on either having reported risk for breast cancer, involvement with other cancer syndromes or were merely plausible given their role in DNA repair pathways. Limiting the results to genes they proposed as clinically actionable decreased the mutation detection rate to 10.6\%, yet the list still included genes with unclear clinical management for breast or other cancers; \textit{BLM}, \textit{MUTYH}, \textit{NBN}, \textit{PRSS1}, \textit{SLX4} (KURIAN, 2014). Management strategies for these patients, and even more so for their relatives found not to share the same mutation, remain unclear. Genetic counselors are often still relying on family history for making surveillance recommendations, though practitioners are inconsistent in determining cancer risk for individuals who test negative for family mutations in genes for which penetrance is not well described in the literature (MCKENNA, 2014).

A review of 2079 patients who had 14-21 gene panel testing performed at Ambry Genetics revealed an overall mutation detection rate of 7-9\%, VUS rate of 15-25\% and normal or uninformative rate of 65-73\%, depending on the panel. They found 3\% of individuals with multiple mutations and 41\% of mutations found were in genes for which no published management guidelines exist (LADUCA, 2014). This group had a rate of \textit{MUTYH} mutation carriers much higher than expected; whether this reflects an increased risk for cancers in this group is unknown. This same commercial laboratory found 7\% of patients with one mismatch repair mutation had a second mutation including \textit{PTEN}, \textit{CHEK2}, \textit{ATM} or \textit{RAD51C}; these patients had extremely variable personal and family cancer histories (SUMMEROUR, 2014). The authors suggest a potential modifying effect of the second mutation on phenotype, with more research required for clarification. In addition, this highlights greater complexity when counseling families about multiplex genetic test results, particularly when determining risk management options for mutation positive and negative individuals (SUMMEROUR, 2014).

Multiplex testing and analysis of moderate and low penetrance genes creates uncertainties in how to apply cancer surveillance strategies that are established for individuals known to be at high risk. The American Cancer Society recommends breast MRI for women at lifetime risk for breast cancer over 20\%, or roughly equivalent to a relative risk of 2 (ACS, 2014). Most USA health care providers recognize this standard, but this guideline has not been universally adopted in Canada. Establishing a specific lifetime
breast cancer risk based on genetic test results is not always straightforward. It remains to be proven if breast MRI is indicated for carriers of \textit{ATM}, \textit{BLM}, \textit{MUTYH} or many of the other genes listed in cancer panels whose relative risks for breast cancer are less well defined and not consistently above 2. Furthermore, specific mutations in a gene and supportive family history are contributing factors to overall risk assessment. While cancer prevention is a noble goal, the unintended harms of doing good should not be overlooked. It remains possible that the risks of screening may outweigh the benefits, as has been reported for ovarian cancer screening (Reade 2013). Over screening for cancer has been shown to lead to over treatment, increased anxiety, decreased quality of life, and even accidental death (MAKARY, 2014).

EVALUATION AND SELECTION OF THE LABORATORY

Once the decision to choose a panel is clear, selecting the laboratory requires significant knowledge. Evaluating laboratory process and outcomes shows that the mutation detection rate from NGS panels differs significantly between laboratories. Detection may be lower or higher than for Sanger sequencing alone. Detection rate is dependent on many factors including depth of coverage (the number of times each base pair is sequenced), and whether deletion/duplication analysis is part of the analysis. One study of 708 suspected hereditary breast cancer patients reported a 15% mutation detection rate using a 16 gene panel with 100% sensitivity for identifying \textit{BRCA1/2} mutations and a 1.8% false positive rate (CASTÉRA, 2014). Another clinical validation study of NGS found 57/59 known mutations in \textit{BRCA1/2} (KURIAN, 2014). Their NGS process had missed a large insertion, while they reported the second “mutation” as a variant of unknown significance (VUS) stating it did not meet current American College of Medical Genetics criteria for pathogenicity (KURIAN, 2014). The analysis did not include deletion/duplication analysis, which likely would have detected the insertion. Further validation by this group on a larger cohort of patients shows 100% specificity and 100% sensitivity for known mutations, inclusive of finding insertions and deletions under 5 base pairs as well as copy-number variations ranging from single exon to whole gene. Improvements were attributed to changes in laboratory protocols and data analysis directed at a combination of read depth variation and split-read analysis (LINCOLN, 2014).

Most commercial laboratories report average read length on their website with 30x coverage a common rate. But knowledge of minimum read length is more important, in addition to knowing how deep sequencing is performed into intron-exon boundaries. One of the largest validation studies to date proved their process had greater sensitivity than Sanger. The investigators used NGS and array CGH for a targeted breast panel composed of 6 well-characterized breast cancer genes. A minimum threshold for depth of coverage for each exon at 50x was set, after which Sanger sequencing was employed. The average sequencing coverage per nucleotide was 9,717x, with no read depths less than 100x. Of 3250 samples analyzed, a 5.7% mutation detection rate, a 10% false positive rate, and a 7.6% VUS rate were reported (CHONG, 2014). This included the identification of two mutations missed by Sanger sequencing. In addition to depth of coverage, the
increased sensitivity was attributed to primer tiling design, which decreased the chance for allele dropout and false negative results caused by polymorphisms located under primer binding sequences. In addition, the primer sequences were eliminated for each read to ensure this data did not dilute out the actual DNA sequence under the primer sites (CHONG, 2014). These validation studies highlight the importance of multiple aspects of laboratory selection including the target enrichment assay, the sequencing technology, minimum depth of coverage and bioinformatics pipeline (CHONG, 2014).

FACILITATING PATIENT DECISION MAKING

Once the genetic practitioner has reviewed the panel testing options, the next challenge is presentation of these options to patients. Incorporating multiplex testing into patient care requires a modified approach to cancer genetic counseling. In a patient-focused decision framework the patient needs to understand the benefits and limitations of their options in order to select the best test. However, genetic counselors tend to be more cautious than the general public with respect to wanting test results that are unclear or involve difficult to interpret information (TOWNSEND, 2012). This is perhaps reflective of the counselors’ experiential understanding of the practical difficulties of dealing with uncertainty, a concept that patients would benefit in understanding in their decision making process. A shared decision making framework may best enable the process of informed choice in the complicated decision for a comprehensive versus a targeted panel; for choosing only highly penetrant, clinically actionable genes or including genes for which we have limited knowledge to direct clinical action (ELWYN, 2000).

In an era of increasing demand for cancer genetic counseling, genetic practitioners need more time to provide appropriate patient care. Current evidence shows significant changes to both the content and length of pre-test genetic counseling appointments, in addition to increased preparation time for appointments and increased need for patient follow-up (HOOKER, 2014; MAUR, 2013; YOUNG, unpublished data). Over 90% of genetic counselors report increased length of pre-test counseling appointments, with more significant increases for discussion of comprehensive panels than for targeted (HOOKER, 20014, YOUNG, unpublished data).

The counseling around a VUS has changed dramatically in order to prepare patients to expect a variant when testing multiple genes (HOOKER, 2014). The majority of counselors surveyed in early 2014 (70%) reported spending more time discussing VUS (YOUNG, unpublished data).

Preparation time for appointments is significantly longer for many reasons. More time is spent considering the multiple laboratory and testing options available (HOOKER, 2014). Significant time is also spent reviewing the literature for penetrance data and management recommendations, particularly in preparation for reporting results. In the absence of published standards significant time is involved in drafting institutional guidelines (MAUR, 2014). In Colorado, USA, a group of genetic counselors created regional practice consensus on these issues for multiple moderate and low penetrance genes through an efficient group evaluation process (SCHNEIDER, 2014). More efficiencies of care are expected to evolve over time.
Questions remain as to how much information a patient needs about each gene on a panel in order to obtain true informed consent but it is generally agreed that detailed cancer risk and management options for all genes is not practical and would likely overwhelm most patients. One strategy is to draw attention to the genes with the highest index of suspicion and then help patients to decide which categories of genes are acceptable to them: highly penetrant genes with guidelines for clinical management, moderately penetrant genes with questionable clinical management options, and low risk genes or those with limited information on both penetrance and clinical management.

A survey of genetic counselors in 2013 identified 25% reviewed high risk syndromes linked to the patient’s indication in detail, 20% presented groups of genes based on risk, and just less than 10% reviewed each individual gene (MCKENNA, 2014). Addressing the general concept of clinical utility for low and moderate risk genes was included by 35% of genetic counselors (YOUNG, unpublished data).

One multidisciplinary team of expert genetic practitioners developed a “tiered and binned” model for obtaining informed consent for multiplex testing in cancer genetic counseling. Information was tiered depending on whether it was deemed essential (Tier 1) or supportive and situationally dependent (Tier 2). Relevant clinical information was then binned to minimize information overload while supporting informed choice. They identified seven Tier 1 elements patients require in order to make informed decisions: testing can identify varying risks; implications of results can vary and finding a mutation may or may not change medical care; evidence in support of management options varies by gene and result; some genes have childhood cancer risks, some in adulthood, some may be associated with other disorders and not all genes are recommended for testing on relatives; there is potential for various uncertainties; testing is a choice; ongoing contact from the patient is recommended as risks and cancer spectrum will change (BRADBURY, 2014). These experts were not able to achieve complete consensus on whether some specific examples of genes and their associated risks should be discussed with patients. Some felt strongly that genes with high risk and limited clinical options, such as TP53 and CDH1 should be used as examples, while others felt the general concepts were sufficient. This is likely to results in variability in clinical care as decisions are based on practitioner preference. More studies are needed to help inform the genetic counseling community on the most effective approach.

Depending on the results of multiplex panel testing, patients may also need to understand the difference between recessive and dominant inheritance and potential risks posed in pregnancy planning as a result of having more than one mutation, eg BRCA and Fanconi Anemia, two PMS2 mutations, or two MUTYH mutations (MAUR, 2014). Furthermore, the implications for family members are more complicated with multiple gene mutations in a family and overlapping phenotypes; results may be more specific to the family history of cancers rather than the published associated cancer risks (BRADBURY, 2014).

In summary, the development of multiplex testing is the most significant factor to have impacted cancer genetic counseling since the identification of BRCA1 and BRCA2. Changing paradigms of genetic counseling are emerging to effectively and efficiently utilize these new tools, with whole exome and whole genome screening...
close on the horizon. Expanded disease phenotypes are emerging, and our understanding of gene penetrance and prevalence is improving. New and more efficient models of genetic health service delivery are needed to ensure patients have adequate access to qualified professionals. The complexity of choices, combined with the variability and uncertainty of results requires educated genetic practitioners to navigate patients through the options and support the ongoing clinical and psychological management of hereditary cancer families.

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Abstract: Panel based genetic testing for hereditary cancer syndromes has recently become available with several international laboratories offering multiple options for the clinician to consider. Genetic Counselors and other health practitioners are faced with new challenges of identifying when to offer a multiplex panel, selecting an appropriate and feasible test, and recommending clinical management strategies based on the results. Interpreting the results in the context of the family history is expanding our understanding of genotype-phenotype correlations, and challenging the application of existing genotype based management guidelines. New models of practice are needed in order to facilitate patient decision-making and informed consent for multiplex testing. This paper explores these issues and the emergence of new paradigms for cancer genetic counseling in the era of multiplex panel testing.

Keywords: Genetic Counselors. Identifying. Clinician

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