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Review of intraoperative parathormone monitoring with the miami criterion: A 25-year experience

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Abstract

With the development of imaging and localization studies, focused parathyroidectomy with use of intraoperative parathormone monitoring (IPM) is the mainstay of treatment for primary hyperparathyroidism at many health care centers both nationally and internationally. Focused parathyroidectomy guided by IPM allows for surgical excision of the offending parathyroid gland through smaller incisions. The Miami criterion is a protocol that uses a "> 50% parathormone (PTH) drop" from either the greatest pre-incision or pre-excision measurement of PTH in a blood sample taken 10 min following resection of hyperfunctioning glands. Following removal of the hyperfunctioning parathyroid gland, a > 50% PTH drop at 10 min indicates completion of parathyroidectomy, and predicts operative success at 6 mo. IPM using the Miami criterion has demonstrated equal curative rates of > 97%, which is comparable to the traditional bilateral neck exploration. The focused approach, however, is associated with shorter recovery times, improved cosmesis, and lower risk of postoperative hypocalcemia.

Key words: Focused parathyroidectomy; Intraoperative parathormone monitoring; Primary hyperparathyroidism; Miami criterion; Localization studies

Core tip: Intraoperative parathormone monitoring (IPM) is vital component of the focused parathyroidectomy, the management of choice for primary hyperparathyroidism at the authors' institution. IPM is used to confirm complete removal of hyperfunctioning glands while preserving any remaining normally functioning glands before the operation is finished, guide the surgeon to continue neck exploration for additional hyperfunctioning glands when the intraoperative parathormone (PTH) levels do not drop sufficiently, identify parathyroid tissue by measurement of intraoperative PTH levels in fine needle aspiration samples, and lateralize hypersecreting parathyroid(s) through differential jugular venous sampling when preoperative localization studies are equivocal.

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BACKGROUND

In 1925, Dr. Felix Mandl performed the first excision of a parathyroid tumor in Vienna on patient Albert Jahne, a 34-year-old tramcar conductor suffering from osteitis fibrosa cystica who was admitted for a femur fracture[1]. Although he initially experienced a benefit from the parathyroidectomy, Jahne subsequently developed recurrent disease, possibly due to parathyroid carcinoma. He underwent reoperation in 1933, but ultimately died of uremia three years after this second surgical exploration[1]. Despite failing to achieve the desired clinical outcome, Jahne's case shifted the practice dogma towards surgery as the management of choice for primary hyperparathyroidism (pHPT). For most of the 19th century, the surgical treatment of pHPT was based on locating the four parathyroid glands intraoperatively and the excision of any grossly enlarged parathyroid glands while leaving all normal-sized glands *in situ*[2,3]. This qualitative approach that requires bilateral neck exploration (BNE) can be problematic, however, since parathyroid gland size and/or color does not always directly correlate to its secretory function[4,5]. If hypersecreting gland(s) are left behind, hypercalcemia will persist. Conversely, if all normal parathyroid glands are excised or their blood supply compromised during extensive BNE, postoperative hypocalcemia and tetany may occur. Today, when performed by experienced endocrine surgeons, BNE yields success rates of 95% to 99%[2,3].

With the advent of preoperative imaging modalities for the localization of hyperfunctioning glands, targeted or focused parathyroidectomy guided by intraoperative parathormone monitoring (IPM) is currently the standard treatment for patients with pHPT at numerous specialized centers both nationally and internationally[6-12]. This focused approach incorporates the common aspects of minimally invasive surgery resulting in limited surgical exploration, reduced operative time and less morbidity for patients with pHPT while maintaining comparable operative success rates to traditional BNE which ranges from 97% to 99%[6-10]. In general, focused parathyroidectomy is performed by creating a transverse cervical incision along the anterior neck which measures from 2 to 4 cm in those patients with one hyperfunctioning parathyroid gland identified by preoperative localization studies, sestamibi (MIBI) and/or ultrasound. When the offending parathyroid gland(s) is excised, an intraoperative parathormone (PTH) assay is used to confirm that there is no remaining hyperfunctioning tissue. When IPM levels drop by > 50%, usually at 10 min following abnormal parathyroid gland removal, the operation is concluded[13]. Focused parathyroidectomy guided by IPM can be achieved with either general or local anesthesia and can be performed in an ambulatory setting.

THE MIAMI CRITERION

In 1990, Irvin *et al*[14] refined and applied the intraoperative PTH immunoradiometric assay for the surgical management of pHPT after an unsuccessful parathyroid operation. His patient, who was the supervisor of the operating rooms, at the University of Miami/Jackson Memorial Hospital, had pHPT, and she approached Irvin to perform the operation. She underwent traditional BNE during which one large parathyroid gland was excised, and a second contralateral parathyroid gland was biopsied and preserved. Postoperatively, however, her serum calcium failed to normalize. Irvin spent the next 4 mo refining an intraoperative PTH assay to allow for results to be obtained within 15 min. He then took her back to the operating room and, by measuring intact PTH levels intraoperatively, was able to confirm removal of any remaining hyperfunctioning parathyroid glands and predict curative resection in this reoperative patient who had an intrathyroidal parathyroid gland in the contralateral lobe that was not appreciated in her initial operation[14].

In 1991, Irvin *et al*[15] would begin using IPM as a routine adjunct to focused parathyroidectomy at the University of Miami to reduce failure rates due to missed multiglandular disease (MGD). Having performed over 700 parathyroidectomies at that time, he attributed his failure rate of 7% to misdiagnosis or inability to excise all hyperfunctioning parathyroid gland tissue[15]. This intraoperative adjunct often termed the "quick PTH assay" takes advantage of the half-life of PTH which is approximately 3 to 5 min. Irvin further refined the PTH assay in 1993 to address the issue of long turnaround time for PTH results, which made previous attempts at intraoperative monitoring less practical[16,17]. Since then, the intraoperative "quick PTH assay" has undergone many modifications since the original immunoradiometric assay developed by Dr. Irvin. In current practice, intraoperative PTH is measured using a rapid immunochemiluminescence assay.

With the success and practicality of the intraoperative quick PTH assay, Irvin went on to describe the Miami criterion, a protocol that uses a "> 50% PTH drop" from either the highest pre-incision or pre-excision PTH measurement in a sample taken 10 min following complete resection of the hyperfunctioning glands. Following removal of the hyperfunctioning parathyroid gland, a > 50% PTH drop at 10 min indicates removal of the abnormal parathyroid glands, predicting operative success at 6 mo[13]. As a result, IPM allows for a focused or targeted approach to parathyroidectomy that involves surgical excision of the offending gland through smaller incisions with equal curative rates of > 97%

which is comparable to BNE[6-10]. The focused approach is also associated with fewer comorbidities including permanent hypoparathyroidism that may result from iatrogenic ischemia or injury to the remaining parathyroids during BNE.

At the University of Miami, the intraoperative PTH assay permits the surgeon to confirm excision of all abnormal parathyroid glands while preserving the remaining normally functioning parathyroid glands before the operation is finished; guide the surgeon to continue neck exploration for additional abnormal glands when the intraoperative PTH levels do not drop sufficiently; distinguish parathyroid from non-parathyroid tissue by measurement of intraoperative PTH levels in fine needle aspiration (FNA) samples; and lateralize hypersecreting parathyroid(s) to either side of the neck through differential jugular venous sampling when preoperative localization studies are equivocal.

IPM IN CURRENT PRACTICE

Surgeons must understand that the intraoperative PTH assay only measures the circulating amount of hormone from the location where blood samples are obtained and direct the sampling times related to the stages of the operative procedure. The "Miami criterion", which uses a "> 50% PTH drop" from either the greatest pre-incision or pre-excision PTH measurement in a sample of blood drawn 10 min following complete resection of a hyperfunctioning gland, requires peripheral venous or arterial access for blood collection at specific times during parathyroidectomy[13,16-18]. Intravenous access is maintained with a slow saline infusion that is discarded from the line to prevent dilution before any blood sample is quantified. Intraoperatively, at least 4 mL of peripheral whole blood sample in an EDTA specimen tube is collected at the following times: (1) a "pre-incision" level prior to skin incision; (2) a "pre-excision" level collected prior to clamping the blood supply to the abnormal gland; (3) a 5-min level; and (4) 10-min level after excision of the abnormal tissue. The samples should be promptly delivered to the laboratory for processing. With the efficiency and speed of the intraoperative PTH assay, point of care testing which measures PTH at the bedside is not performed at this institution.

When the PTH levels drop > 50% from the highest pre-incision or pre-excision value 10 min following the removal of the hyperfunctioning gland, this criterion predicts normal or low calcium measurements postoperatively with an overall accuracy of 98%[13]. After this "> 50% PTH drop" occurs, the surgeon terminates the operation without further identification of the normal parathyroid glands that remain. In the event that the PTH level at 10 min does not meet this criterion, an additional level may be obtained at 20 min and/or additional neck exploration can be performed until the removal of the remaining hyperfunctioning glands is determined by > 50% PTH drop from the highest subsequent pre-excision PTH measurement[19].

INTERPRETATION OF IPM DYNAMICS

A thorough knowledge of the disease process and careful interpretation of intraoperative PTH dynamics is required to effectively guide the surgeon during parathyroidectomy. The first example is of a 58-years-old woman with biochemical evidence confirming pHPT who presented with a PTH measurement of 107 pg/mL and a calcium level of 11.1 mg/dL on routine blood testing (Figure 1A). Her Tc-99m-sestamibi and ultrasound scans were concordant and suspicious for a right inferior parathyroid gland. An abnormal right inferior parathyroid was visualized intraoperatively, and this gland was carefully removed. Intraoperative PTH levels were drawn with the following measured values: Pre-incision 142 pg/mL; pre-excision 59 pg/mL; at 5 min 33 pg/mL, and at 10 min 25 pg/mL. The drop in Pre-excision level suggests the surgeon has identified the hyperfunctioning parathyroid gland as reflected in the > 50% PTH drop, which predicts operative success.

The next example is of a 45-year-old gentleman with biochemical confirmation of pHPT who presented with a calcium level of 10.8 mg/dL and PTH level of 125 pg/mL on routine blood tests (Figure 1B). His MIBI and ultrasound studies were concordant for a suspicious left inferior parathyroid. Intraoperatively, an abnormal left inferior parathyroid gland was located and excised with intraoperative PTH levels measured as follows: Pre-incision 109 pg/mL; pre-excision 170 pg/mL; at 5 min 51 pg/mL, and at 10 min 34 pg/mL. Unlike in the first case, the dramatic rise in pre-excision level, which was not observed in the previous example, suggests the surgeon has identified the hyperfunctioning parathyroid gland. During dissection, manipulation of the abnormal gland by the surgeon may have resulted in a sudden surge of PTH into the bloodstream reflected by a dramatic rise of pre-excision PTH level, it is important in this scenario to witness a drop in the PTH level on the subsequent 5 and 10 min samples. The patient's values ultimately reflect a > 50% PTH drop when compared to the pre-incision PTH level.

The final scenario is of a 34-years-old man who arrived to the emergency room with kidney stones (Figure 2). As a part of his evaluation, an elevated calcium level of 11 mg/dL and parathyroid hormone level of 119 pg/mL were measured. A preoperative MIBI scan did not localize an abnormal parathyroid gland. Following the excision of a right inferior parathyroid gland, intraoperative PTH levels drawn were: Pre-incision 173 pg/mL; pre-excision 150 pg/mL; at 5 min 143 pg/mL, and at 10 min 135 pg/mL. Without a > 50% PTH drop, exploration continued contralaterally and an abnormal left inferior parathyroid gland was discovered and excised. Intraoperative PTH levels were again measured and were as follow: Pre-excision 137 pg/mL; at 5 min 27 pg/mL; and at 10 min 19 pg/mL, confirming removal of hyperplastic parathyroid tissue

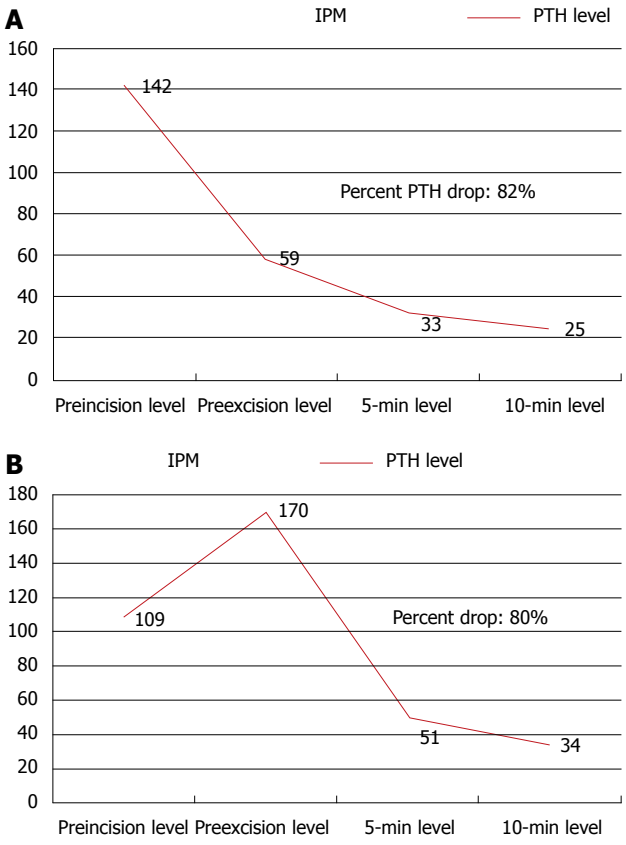

Figure 1 Intraoperative parathormone monitoring dynamics demonstrating a > 50% drop when compared to the pre-incision parathormone level using the Miami criterion. A: The drop of pre-excision PTH level suggests that the surgeon identified the hyperfunctioning gland during dissection reflected in the drop of PTH level; B: During dissection, manipulation of the abnormal gland may result in a release of PTH into the bloodstream, reflected by a surge in PTH level. It is important in this scenario to observe a drop in the PTH level on the subsequent 5 and 10 min samples from the higher pre-excision PTH level. IPM: Intraoperative parathormone monitoring; PTH: Parathormone.

with a > 50% PTH drop. As demonstrated in this case, when the PTH level fails to decrease > 50% from either highest pre-incision or pre-excision level, there should be a suspicion for MGD.

OTHER USES OF INTRAOPERATIVE PTH MEASUREMENT

Biochemical FNA

FNA of tissue for PTH measurement has valuable use in differentiating parathyroid glands from other tissues. During BNE or focused parathryoidectomy, biochemical FNA may be of value in identifying parathyroid tissue *vs* other tissues within the neck. When trying to differentiate between parathyroid from thyroid tissue or lymph nodes, this technique may be very helpful to the surgeon. A sample is obtained using a 25 gauge needle and diluted in 1 mL of normal saline. The sample is then sent to the laboratory where it is centrifuged. The PTH level is measured from the remaining supernatant after centrifugation[20]. As biochemical FNA has 100% specificity, this intraoperative technique can confirm parathyroid tissue more expeditiously than frozen section.

Internal jugular venous sampling

In the setting of discordant or negative preoperative localization imaging, differential venous sampling using the intraoperative PTH assay may allow surgeons to perform unilateral neck exploration in patients rather than BNE[21-23]. In order to lateralize the hyperfunctioning gland, bilateral internal jugular venous sampling of PTH is effective in directing surgical exploration. This procedure can be safely performed with ultrasound guided sampling of the inferior right and left internal jugular veins prior to skin incision. When there is a greater than 5% to 10% difference in PTH level, laterality to the side of the hyperfunctioning gland can be determined[21,22]. The surgeon may begin the operation by first exploring the identified side of the neck. The sensitivity of differential venous sampling approaches 80% according to published studies[21,22].

IPM and discordant localization studies

It has been argued that with the advancements in imaging modalities, combined preoperative localization with technetium Tc 99m sestamibi and ultrasound may eliminate need for IPM. In one retrospective cohort study of 569 patients with pHPT who underwent both MIBI and ultrasound, only 57% (n = 322) of patients had preoperative concordant localization studies and, in this group, there was a 99% success rate in achieving postoperative eucalcemia[24]. However, in 35% (n = 201) of patients with only one of two localization studies identifying an abnormal gland, neither MIBI nor ultrasound alone were able to correctly predict the location or extent of disease in 38% (76/201) patients in this discordant group. While there was marginal benefit among patients who had concordant preoperative localization imaging studies, IPM remained vital for patients with discordant studies undergoing limited parathyroidectomy[24]. In a retrospective series of 225 patients with pHPT where operative success was 97%, IPM remained an important adjunct for performing targeted parathyroidectomy in patients with discordant localization studies[25]. In a subgroup of 85 patients (38%) with discordant preoperative imaging, where IPM altered operative management and helped the surgeon during parathyroidectomy, operative success was 93%. In this series, IPM allowed surgeons to perform unilateral operation in 66% of patients, and confirmed excision of hyperfunctioning parathyroid glands in 7 patients with MGD[25].

LONG TERM OUTCOMES FOR IPM GUIDED PARATHYROIDECTOMY

Since 1993, parathyroidectomy has been guided by IPM for patients with pHPT at the University of Miami. BNE is no longer the initial approach in these patients with pHPT unless preoperative localization studies are negative or

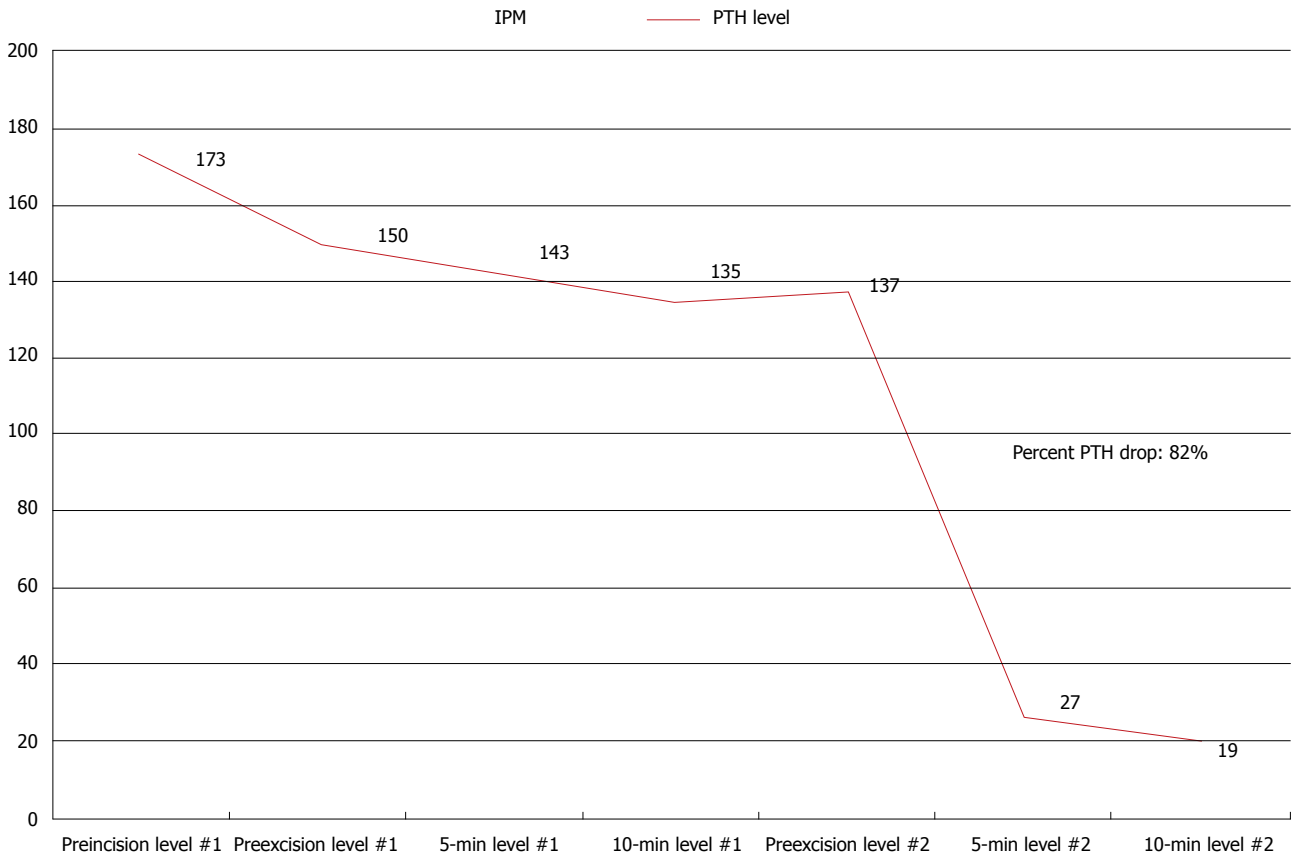

Figure 2 Intraoperative parathormone monitoring dynamics demonstrating > 50% drop using the Miami criterion when more than one abnormal parathyroid gland is removed. When the PTH level fails to drop > 50% from either pre-incision or pre-excision levels, there should be a suspicion for MGD. IPM: Intraoperative parathormone monitoring; MGD: Multiglandular disease; PTH: Parathormone.

when preoperative imaging has identified the wrong side of the neck. At the authors' institution, operative success is defined as calcium levels within normal limits for > 6 mo following successful parathyroidectomy. The definition of operative failure is persistent elevated PTH and elevated calcium measurements occurring < 6 mo following focused parathyroidectomy. Disease recurrence is defined as elevated PTH and elevated calcium measurements occurring > 6 mo following succes sful parathyroidectomy. The definition of MGD is two or more hypersecreting parathyroid glands identified intraoperatively during parathyroidectomy as demonstrated by IPM or if excision of one gland results in operative failure.

While criteria for IPM may vary among surgeons, the principle remains the same. By obtaining PTH levels in real time and achieving a desired reduction, the surgeon may have greater confidence intraoperatively that the offending hyperfunctioning parathyroid gland has been excised. While IPM has become common practice in most experienced centers, the Miami criterion has been compared to other stricter protocols in predicting post-operative eucalcemia. Stricter criteria proposed include a larger > 65%-70% PTH drop and/or return of absolute PTH level to within normal limits, or a PTH decrease at 5 min after gland removal[26-28]. In comparison to other criteria, the > 50% PTH drop was found to accurately predict operative success in > 95% of patients who had IPM guided parathyroidectomy for pHPT. In fact, the Miami criterion demonstrated the highest accuracy in predicting operative success when compared to other protocols, which included the Vienna, Rome, and Halle criteria[27]. In a study, which applied stricter protocols, the false positive rate would be reduced; however, at the expense of a lower sensitivity and an increased false negative rate. This false negative rate would then result in performance of BNE not necessary for the patient[29].

An additional protocol from the Mayo clinic was compared to different criteria in a study of 1882 patients with pHPT who had parathyroidectomy with IPM[30]. The Mayo criterion defined a successful parathyroidectomy as > 50% from baseline in addition to a normal or near-normal intraoperative PTH measurement at 10 min following removal of the abnormal gland. The Mayo criterion was compared with the following criteria for monitoring: A > 50% PTH drop at 10 min, > 50% PTH drop at 5 min, and intraoperative PTH within normal range at 10 min. The authors described an operative success of 97% equivalent to that of the Miami criterion. Results were similar when comparing Mayo criterion which had a sensitivity of 96%, PPV of 99%, and an accuracy of 95%, whereas the Miami criterion had had a sensitivity of 96%, PPV of 97%, and an accuracy of 94%. The criterion, however, differed with respect to

MGD. Authors reported that MGD was found in 271 patients (14.5%). A total of 134 of 1858 patients (7.2%) were not able to meet criteria predictive of cure, which indicated the presence of MGD. The authors reported that using the > 50% PTH criterion alone would have theoretically resulted in a failed parathyroidectomy in 22.4% of patients affected with MGD[30].

Critics of the focused parathyroidectomy predicted that the combination of both preoperative localization imaging studies and IPM would miss abnormal parathyroid glands, resulting in greater recurrence rates in patients undergoing parathyroidectomy. In a study of simulated focused parathyroidectomy, both preoperative sestamibi and ultrasound for localization and IPM were performed in all 916 patients with pHPT[31]. All patients underwent BNE, 16% of which had additional enlarged parathyroid glands. The researchers determined that the long term failure or recurrence rate of the focused approach may be greater than initially described in previous studies[31]. Other studies, however, demonstrated that focused parathyroidectomy had long-term surgical success that was similar to BNE. In another study of the 181 patients who underwent image-guided parathyroidectomy, no patients developed recurrent disease with a mean follow-up of approximately 5 years[32]. In a randomized clinical trial which had a five year follow-up, recurrence rates for targeted parathyroidectomy and traditional approach were 5% and 3%, respectively[30]. A study of 164 patients with an average follow-up of close to seven years demonstrated a 3% disease recurrence rate following successful focused parathyroidectomy guided by IPM[33]. Additionally, other studies found that parathyroid gland size or pathology do not show a correlation with PTH secretion reliably, as a result they may not be useful indicators for identifying hyperfunctioning parathyroid glands[4,5,34]. Together, such findings demonstrate that the focused parathyroidectomy has a durable operative success rate and does not miss MGD as a cause of disease recurrence. These postoperative outcomes indicate that IPM guided parathyroidectomy may allow for minimal dissection for patients with single gland disease in pHPT with durable long-term eucalcemia.

The implementation of IPM in patients with pHPT has shifted the surgical approach to parathyroidectomy from BNE to less invasive operations. Many studies have confirmed that the success of focused parathyroidectomy guided by IPM demonstrate operative success rates comparable to conventional BNE[6-10]. One study of 718 patients over thirty-four years demonstrated rates of operative success for focused parathyroidectomy and traditional approach to be 97% and 94%, respectively[6]. A review of 656 patients with 255 undergoing focused parathyroidectomy and 401 undergoing BNE demonstrated success rates of 99% and 97%, respectively[8]. The overall rates of complications for focused parathyroidectomy and BNE within this same study were 1.2% and 3%, respectively[8]. Patients who underwent focused parathyroidectomy experienced reduced operating room times of 1.3 h in contrast to patients undergoing BNE with operating times of 2.4 h[8]. There were shorter hospitalizations of 0.24 d for focused parathryoidectomy in comparison to 1.64 d for BNE[8]. Focused parathyroidectomy demonstrated equivalent long-term results when compared to conventional BNE for patients with pHPT in one randomized controlled trial with a 5-year follow-up[35].

CONCLUSION

Over the past 25 years, IPM has been an effective surgical adjunct that can be of help during parathyroidectomy in patients with pHPT. IPM has been shown to effectively confirm operative success with a focused or targeted approach that allows for minimal dissection and selected parathyroid gland excision. Using the Miami or "> 50% PTH drop" criterion, the surgeon excises only the hyperfunctioning parathyroid gland(s) without identifying the remaining normal parathyroid glands. Instead of identifying abnormal parathyroid glands by size, color, and/or pathology, IPM allows for quantitative recognition of parathyroid gland hyperfunction based on PTH secretion during parathyroidectomy where pHPT is recognized as a disease of function rather than form. IPM guided parathyroidectomy has become the preferred initial approach over traditional BNE, and there has been a shift of treatment paradigm from comprehensive to limited parathyroidectomy for pHPT over the last few decades. Parathyroidectomy guided by IPM has evolved into a highly successful and rapid operation, usually requiring minimal dissection that can be performed in an ambulatory setting. IPM has proven to be a vital adjunct to focused parathyroidectomy demonstrated by its high postoperative success rate and long term outcomes, and its efficacy ensures that this important tool will continue to benefit surgeons in the future.

REFERENCES

1 **Niederle BE**, Schmidt G, Organ CH, Niederle B. Albert J and his surgeon: a historical reevaluation of the first parathyroidectomy. *J Am Coll Surg* 2006; **202**: 181-190 [PMID: 16377512 DOI: 10.1016/j.jamcollsurg.2005.03.036]

2 **Kaplan EL**, Yashiro T, Salti G. Primary hyperparathyroidism in the 1990s. Choice of surgical procedures for this disease. *Ann Surg* 1992; **215**: 300-317 [PMID: 1558410]

3 **Allendorf J**, DiGorgi M, Spanknebel K, Inabnet W, Chabot J, Logerfo P. 1112 consecutive bilateral neck explorations for primary hyperparathyroidism. *World J Surg* 2007; **31**: 2075-2080 [PMID: 17768656]

4 **Mun HC**, Conigrave A, Wilkinson M, Delbridge L. Surgery for hyperparathyroidism: does morphology or function matter most? *Surgery* 2005; **138**: 1111-120; discussion 1120 [PMID: 16360398 DOI: 10.1016/j.surg.2005.09.015]

5 **Elliott DD**, Monroe DP, Perrier ND. Parathyroid histopathology: is it of any value today? *J Am Coll Surg* 2006; **203**: 758-765 [PMID: 17084340 DOI: 10.1016/j.jamcollsurg.2006.07.031]

6 **Irvin GL**, Carneiro DM, Solorzano CC. Progress in the operative management of sporadic primary hyperparathyroidism over 34 years. *Ann Surg* 2004; **239**: 704-708; discussion 708-711 [PMID: 15082975 DOI: 10.1097/01.sla.0000124448.49794.74]

7 **Westerdahl J**, Lindblom P, Bergenfelz A. Measurement of intraoperative parathyroid hormone predicts long-term operative success. *Arch Surg* 2002; **137**: 186-190 [PMID: 11822958 DOI: 10.1001/archsurg.137.2.186]

8 **Udelsman R**. Six hundred fifty-six consecutive explorations for primary hyperparathyroidism. *Ann Surg* 2002; **235**: 665-670; discussion 670-672 [PMID: 11981212]

9 **Chen H**, Pruhs Z, Starling JR, Mack E. Intraoperative parathyroid hormone testing improves cure rates in patients undergoing minimally invasive parathyroidectomy. *Surgery* 2005; **138**: 583-587; discussion 587-590 [PMID: 16269285 DOI: 10.1016/j.surg.2005.06.046]

10 **Grant CS**, Thompson G, Farley D, van Heerden J. Primary hyperparathyroidism surgical management since the introduction of minimally invasive parathyroidectomy: Mayo Clinic experience. *Arch Surg* 2005; **140**: 472-478; discussion 472-478 [PMID: 15897443 DOI: 10.1001/archsurg.140.5.472]

11 **Sackett WR**, Barraclough B, Reeve TS, Delbridge LW. Worldwide trends in the surgical treatment of primary hyperparathyroidism in the era of minimally invasive parathyroidectomy. *Arch Surg* 2002; **137**: 1055-1059 [PMID: 12215160 DOI: 10.1001/archsurg.137.9.1055]

12 **Greene AB**, Butler RS, McIntyre S, Barbosa GF, Mitchell J, Berber E, Siperstein A, Milas M. National trends in parathyroid surgery from 1998 to 2008: a decade of change. *J Am Coll Surg* 2009; **209**: 332-343 [PMID: 19717037 DOI: 10.1016/j.jamcollsurg.2009.05.029]

13 **Carneiro DM**, Solorzano CC, Nader MC, Ramirez M, Irvin GL. Comparison of intraoperative iPTH assay (QPTH) criteria in guiding parathyroidectomy: which criterion is the most accurate? *Surgery* 2003; **134**: 973-979; discussion 973-979 [PMID: 14668730]

14 **Irvin GL**. American Association of Endocrine Surgeons. Presidential address: chasin' hormones. *Surgery* 1999; **126**: 993-997 [PMID: 10598178]

15 **Irvin GL**, Dembrow VD, Prudhomme DL. Operative monitoring of parathyroid gland hyperfunction. *Am J Surg* 1991; **162**: 299-302 [PMID: 1683177]

16 **Irvin GL**, Dembrow VD, Prudhomme DL. Clinical usefulness of an intraoperative "quick parathyroid hormone" assay. *Surgery* 1993; **114**: 1019-1022; discussion 1022-1023 [PMID: 8256205]

17 **Irvin GL**, Deriso GT. A new, practical intraoperative parathyroid hormone assay. *Am J Surg* 1994; **168**: 466-468 [PMID: 7977975]

18 **Irvin GL**, Sfakianakis G, Yeung L, Deriso GT, Fishman LM, Molinari AS, Foss JN. Ambulatory parathyroidectomy for primary hyperparathyroidism. *Arch Surg* 1996; **131**: 1074-1078 [PMID: 8857905 DOI: 10.1001/archsurg.1996.01430220068015]

19 **Irvin GL**, Solorzano CC, Carneiro DM. Quick intraoperative parathyroid hormone assay: surgical adjunct to allow limited parathyroidectomy, improve success rate, and predict outcome. *World J Surg* 2004; **28**: 1287-1292 [PMID: 15517474 DOI: 10.1007/s00268-004-7708-6]

20 **Perrier ND**, Ituarte P, Kikuchi S, Siperstein AE, Duh QY, Clark OH, Gielow R, Hamill T. Intraoperative parathyroid aspiration and parathyroid hormone assay as an alternative to frozen section for tissue identification. *World J Surg* 2000; **24**: 1319-1322 [PMID: 11038200]

21 **Taylor J**, Fraser W, Banaszkiewicz P, Drury P, Atkins P. Lateralization of parathyroid adenomas by intra-operative parathormone estimation. *J R Coll Surg Edinb* 1996; **41**: 174-177 [PMID: 8763181]

22 **Udelsman R**, Osterman F, Sokoll LJ, Drew H, Levine MA, Chan DW. Rapid parathyroid hormone measurement during venous localization. *Clin Chim Acta* 2000; **295**: 193-198 [PMID: 10767405 DOI: 10.1016/S0009-8981(00)00184-4]

23 **Ito F**, Sippel R, Lederman J, Chen H. The utility of intraoperative bilateral internal jugular venous sampling with rapid parathyroid hormone testing. *Ann Surg* 2007; **245**: 959-963 [PMID: 17522522 DOI: 10.1097/01.sla.0000255578.11198.ff]

24 **Gawande AA**, Monchik JM, Abbruzzese TA, Iannuccilli JD, Ibrahim SI, Moore FD. Reassessment of parathyroid hormone monitoring during parathyroidectomy for primary hyperparathyroidism after 2 preoperative localization studies. *Arch Surg* 2006; **141**: 381-384; discussion 384 [PMID: 16618896 DOI: 10.1001/archsurg.141.4.381]

25 **Lew JI**, Solorzano CC, Montano RE, Carneiro-Pla DM, Irvin GL. Role of intraoperative parathormone monitoring during parathyroidectomy in patients with discordant localization studies. *Surgery* 2008; **144**: 299-306 [PMID: 18656639 DOI: 10.1016/j.surg.2008.03.039]

26 **Chiu B**, Sturgeon C, Angelos P. Which intraoperative parathyroid hormone assay criterion best predicts operative success? A study of 352 consecutive patients. *Arch Surg* 2006; **141**: 483-47; discussion 483-487 [PMID: 16702520 DOI: 10.1001/archsurg.141.5.483]

27 **Barczynski M**, Konturek A, Hubalewska-Dydejczyk A, Cichon S, Nowak W. Evaluation of Halle, Miami, Rome, and Vienna intraoperative iPTH assay criteria in guiding minimally invasive parathyroidectomy. *Langenbecks Arch Surg* 2009; **394**: 843-849 [PMID: 19529957 DOI: 10.1007/s00423-009-0510-z]

28 **Clerici T**, Brandle M, Lange J, Doherty GM, Gauger PG. Impact of intraoperative parathyroid hormone monitoring on the prediction of multiglandular parathyroid disease. *World J Surg* 2004; **28**: 187-192 [PMID: 14708048 DOI: 10.1007/s00268-010-0887-4]

29 **Carneiro-Pla DM**, Solorzano CC, Lew JI, Irvin GL. Long-term outcome of patients with intraoperative parathyroid level remaining above the normal range during parathyroidectomy. *Surgery* 2008; **144**: 989-993; discussion 993-994 [PMID: 19041008 DOI: 10.1016/j.surg.2008.08.026]

30 **Richards ML**, Thompson GB, Farley DR, Grant CS. An optimal algorithm for intraoperative parathyroid hormone monitoring. *Arch Surg* 2011; **146**: 280-285 [PMID: 21422358 DOI: 10.1001/archsurg.2011.5]

31 **Siperstein A**, Berber E, Barbosa GF, Tsinberg M, Greene AB, Mitchell J, Milas M. Predicting the success of limited exploration for primary hyperparathyroidism using ultrasound, sestamibi, and intraoperative parathyroid hormone: analysis of 1158 cases. *Ann Surg* 2008; **248**: 420-428 [PMID: 18791362 DOI: 10.1097/SLA.0b013e3181859f71]

32 **Sidhu S**, Neill AK, Russell CF. Long-term outcome of unilateral parathyroid exploration for primary hyperparathyroidism due to presumed solitary adenoma. *World J Surg* 2003; **27**: 339-342 [PMID: 12607063]

33 **Lew JI**, Irvin GL. Focused parathyroidectomy guided by intraoperative parathormone monitoring does not miss multiglandular disease in patients with sporadic primary hyperparathyroidism: a 10-year outcome. *Surgery* 2009; **146**: 1021-1027 [PMID: 19879612 DOI: 10.1016/j.surg.2009.09.006]

34 **Carneiro-Pla DM**, Romaguera R, Nadji M, Lew JI, Solorzano CC, Irvin GL. Does histopathology predict parathyroid hypersecretion and influence correctly the extent of parathyroidectomy in patients with sporadic primary hyperparathyroidism? *Surgery* 2007; **142**: 930-935; discussion 930-935 [PMID: 18063078 DOI: 10.1016/j.surg.2007.09.019]

35 **Westerdahl J**, Bergenfelz A. Unilateral versus bilateral neck exploration for primary hyperparathyroidism: five-year follow-up of a randomized controlled trial. *Ann Surg* 2007; **246**: 976-980; discussion 980-981 [PMID: 18043099]

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MINIREVIEWS

Patient handoffs in surgery: Successes, failures and room for improvement

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Abstract

Patient handoffs are transitions where communication failures may lead to errors in patient care. Face-to-face handoffs are preferred, however may not always be feasible. Different models and strategies have been described, yet there are few experimental studies. Expanding the problem, the on-call surgeon may be responsible for many patients, few or none that they admitted. Effective handoffs improve the quality of care and result in fewer errors. Herein we review different models of patient handoffs, comment on common pitfalls, and suggest areas for new research.

Key words: Patient handoff; Communication; Patient handover; Patient care; Face-to-face communication; Check out; Sign out

Core tip: Effective handoffs facilitate effective patient care. Distractions during handoffs cause errors in care, there are no outcomes data to recommend one type of handoff over another, and one type of handoff cannot satisfy all types of practice, even within the same institution.

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INTRODUCTION

Handoffs of patient care represent transition points where poor communication may lead to errors. The on-call surgeon may be responsible for many patients, few or none of whom they admitted. Communication barriers are the most frequent cause of handoff errors and may lead to adverse patient events[1]. Previous studies have demonstrated that there is omission of essential

patient information in up to 60% of handoffs[2,3]. Academic centers have faced challenges with handoffs since the implementation of the 80-h work week with more transitions in patient care[4]. With these work-restrictions and changes in health care economics and structure, there is a tendency towards more shift work, night team models, and cross coverage, thus reducing the continuity of care with the admitting physician or team. While reduced work hours may improve lifestyle, patient management can be compromised by communication errors and patient unfamiliarity. There is a paucity of studies that focus on physician-to-physician communication for transfer of patient care compared to the wealth of literature that addresses physician to patient communication[5,6]. Herein, we review the current status, pitfalls, and problems in patient handoffs.

Handoff definition

Although the meaning of a "handoff' is considered implicit by many, no common definition exists in the literature. Efforts have been taken to standardize the definition to facilitate data collection and research, but there is still no consensus[7]. Difficulties in standardizing a definition stem from what to include and exclude. Department- and hospital-specific needs differ considerably; for example, the essential information in a pediatric ward would be very different than that of a surgical intensive care unit. Cohen *et al*[7] provide one definition, "the exchange between health professionals of information about a patient accompanying either a transfer of control over, or of responsibility for, the patient". The Joint Commission defines the handoff process as a session "in which information about patient/client/resident care is communicated in a consistent manner"[8]. For the present work, we define a handoff as an on-call surgeon assuming the temporary care of another surgeon's patient - a vulnerable process that can be compromised by communication failures or individual errors.

Standardization of handoffs

Given that communication errors are well-known consequences of handoffs, the Joint Commission recommends standardization of handoffs; however, they do not provide examples or templates[7]. Similarly, many organizations recommend a standardized approach for patient handoffs, yet fail to provide any examples or what constitutes an effective handoff; one extensive review of the handoff literature failed to find a single instance of an organization providing a template for ideal handoffs[7]. Physicians seem to be amenable to standardized handoffs. In one survey study of emergency medicine program directors, the majority (72.3% of 185) agreed that a standardized handoff system may reduce errors, but most did not have standard policies in their own institution[9]. Data that show standardizations in handoffs improve patient outcomes are lacking. Any data that demonstrated the value of standardization would likely promote implementation. Changing well-established, individualized physician or service handoff practices to a standardized institutional handoff policy may impair, rather than improve efficiency since hospitals, units, and levels of care are vastly different. Given this, the majority of research on handoffs focuses on improvement within a single unit[1]. The on-call surgeon's burdens can be tremendous, especially with cross coverage with trauma and/or acute care surgery. Any process to standardize the handoff process would presumably improve patient care, although these processes should be individualized to particular institutions.

Surgical patient susceptible to errors in handoffs

The surgical patient is uniquely vulnerable to handoff errors because of the transient nature of their care, including the preoperative, perioperative, and postoperative transitions of care. There is a paucity of experimental surgery-specific studies on handoffs - Table 1 highlights some selected surgical studies. One study of 20 patients undergoing major gastrointestinal surgeries found a degradation in the transfer of patient information as the patients went from one phase of care to another[10]. There were failures of communication along all phases of care from preoperative period to postoperative handoffs, both of which had the highest number of communication failures. Fifteen of the 20 patients in that study had minor incidents or adverse events stemming from communication failures. Such errors may sometimes be due to differences in workflow as care is passed from the surgeon to the anesthesiologist and then back again to the surgeon on the wards or intensive care unit[2,10].

Concerning surgeon-to-surgeon handoffs, one study found that 28% of 146 patient adverse incidents in surgical care were attributed to handoffs[11]. Handoffs may not accurately identify problematic patients. One study that followed the sign-out sheets of one surgical residency program found that only 42% of adverse event occurred in patients identified as problematic - patients assigned to the on call team, believing they may be subject to complications[12]. As stated, surgical patients are inherently vulnerable to errors in handoffs with a high number of transitions in the preoperative, perioperative, to postoperative care periods. In addition, night float models often task the resident or attending surgeon to bear responsibility for many patients. In these settings, problems accumulate and are prioritized. The addition of a few urgent or emergent trips to the operating room leads to more opportunities for compromises in care. Prioritizing whether a patient with sudden shortness of breath *vs* another patient in the emergency room with pneumoperitoneum from a perforated ulcer deserves the on call surgeon's attention, all the while remember to check on yet another patient's serial cardiac enzymes is an example of the difficulty of the night float system.

Duty hours in residency programs

Since the implementation of the 80-h work week in

Table 1 Selected surgical handoff studies

Ref.	Design	Methods	Results
Johner *et al*[18]	Multi-center survey	Handoff practices of acute care surgery service in six Canadian general surgery residency programs	39 of 52 surveyed responded. 60% handoffs were mostly are always conducted face to face. Vast majority involved some kind of verbal communication
Zavalkoff *et al*[25]	Single-center implementation of handoff tool	Assess if implementing fill-in-the-blank handoff tool for pediatric heart surgery patients going to intensive care unit improved communication and adverse events	31 handoffs analyzed compared to handoffs prior to sheet. Following implementation of the tool, increase in detail of useful information transfer, no significant increase in time for handoff, lower rate of adverse events but did not reach significance
Scoglietti *et al*[12]	Single-center analysis of sign-out sheets	Resident sign-out sheets, which stratified problematic *vs* non-problematic patients, were collected over a 3-mo period. Patient outcome was analyzed	More non-problematic patients had adverse events, only 42% of adverse events occurred in the problematic patients
Al-Benna *et al*[19]	Multi-center telephone questionnaire	Handoff practices and quality by queried trainee surgeons at 30 British Isles burns units	Majority of units had junior-to-junior handoffs (76.7%), senior-to-senior trainee handoff (56.7%), and more than one level of trainee present. Few handoffs sessions were pager-free of interruptions (10%) and few had formal handoff training (16.7%)
Gawande *et al*[11]	Multi-center interviews	Interview of 38 surgeons from three academic teaching hospitals to identify errors that led to patient incidents	145 incidents reported, 43% (n = 62) of which were due to communication breakdown; of these 66% (n = 41) were due to handoffs errors

2003, general surgery residency programs have been challenged with developing schedules to minimize transitions in patient care. Night teams, float systems, and cross coverage have been implemented to adhere to the duty hour restrictions. This has caused a shiftwork mentality in some programs[4]. A study of malpractice claims showed that handoff errors are more common in teaching institutions[13]. Whether these errors are from ineffective handoffs or too many patients for the on-call resident to adequately care for, the end result is a resident unfamiliar with the patients and their specific needs[14]. Addressing these concerns, an Accreditation Council for Graduate Medical Education task force has made recommendations for residency programs to provide formal instructions for patient handoffs[4]. These include: Schedule designs to minimize the number of handoffs, offer clear documentation on how the handoff process is conducted, and make available the schedules of responsible residents and attendings[15]. Twenty-two of 29 surgical residents stated they perceived that patient care has been compromised by duty hour restrictions, however with improved perception of residents' quality of life[16]. Compromises in the continuity of care, a negative view of the night float system, and decreasing resident work ethics were major factors identified for decreased quality of patient care. The Johns Hopkins surgical residency program emphasizes a 10-point system for an effective handoff. Selected aspects of this 10-point system include: (1) allot adequate time for handoffs; (2) make the process active; (3) emphasize critically ill patients; (4) identify the chief resident on-call; and (5) only have a single standardized list[17]. Whether perception or reality that the limited work week compromises patient care, work hour restrictions is the system we are given - efforts must be made to optimize handoffs to improve the continuity of patient care.

Models of handoffs

There are several different models of handoffs, including, but not limited to, face-to-face and computer-assisted handoffs. Johner *et al*[18] reported a multi-institutional survey which queried handoff practices of acute care surgery service in six Canadian general surgery residency programs. They found that 60% of handoffs were mostly, or completely, conducted face to face. Further, the vast majority involved some form of verbal communication. However, these handoffs were rarely conducted in a quiet or private setting and over 25% of the time was interrupted. Another study surveyed surgeon trainees in 30 different burn units in the British Isles and found that the majority of units had junior to junior trainee handoffs (76.7%), senior to senior trainee handoff (56.7%), and more than one level of trainee present. Few handoffs sessions were free of pager interruptions (10%) and few participants had formal handoff training (16.7%)[19]. One study, evaluating internal medicine residents in four different hospitals, concluded that face-to-face handoffs are best for effectively communicating and reducing errors. Schouten *et al*[20] conducted a retrospective review that compared 305 patients who had a face-to-face handoff compared to 500 patients who were handed over using other methods. In their study, they found no difference in adverse events or mortality between the two groups. They hypothesize that providers that did not receive a dedicated face-to-face handoff may have spent more time familiarizing themselves with patients through other means. They also challenge the importance of face-to-face handoffs in a system where electronic medical records make all data available at one's disposal. Some authors advocate the use of computer-assisted handoffs. Flanagan *et al*[21] conducted a study with 35 internal medicine resident physicians in which computerized patient data were used to generate an electronic patient handoff tool. The objectives of this preliminary study included assessment of the completeness of the tool and the need for more information by the receiving physician. Findings

included that, often times, the report did not include the assessment and plan, and, in many cases, certain data were not accurately transferred. Distractions during handoffs increase the chance that working memory will fail, leading to a higher chance of subsequent medical errors[22]. Although face-to-face handoffs are felt to improve the receiving physician's perception of quality[23], data have not proven that face-to-face handoffs are associated with better patient outcome.

Current and future handoff research

Riesenberg *et al*[1] conducted a systematic review of physician handoffs in the United States. Their search yielded 46 articles, 33 of which were published since 2005. Only 18 of these 46 articles were experimental with the remainder being anecdotal experience, reviews, *etc.* Furthermore, their review revealed that only 6 of the 18 research articles had some measure of handoff effectiveness. Their study found that communication was the most frequently identified barrier to effective handoffs. Forty-five of forty-six articles involved residents or had a medical education theme. The status, problems, and differences in community hospitals are largely not reported in the literature[2]; this represents an area for future research.

One subject the literature on handoffs has yet to explore is the use of texting in communicating patient related care. The use of texting to communicate among residents and attendings was demonstrated in a single center survey study by Shah *et al*[24]. By surveying residents and attendings, they found that the majority of both residents (66%) and attendings (62%) used texting for patient-related care. Verbal or phone conversations were used more often for urgent or emergent situations, however, text messages were the primary means of communication of day-to-day practice of routine patient care. That study did not specifically address handoffs and there are no studies that we are aware of that have done so. Texting prevalence and other uses of smartphones in handoffs and comparison to other means would be a useful contribution to the literature.

CONCLUSION

From the literature, there is much stress on the importance of effective handoffs, yet few scientific studies. Several principles are clear: (1) distractions during handoffs cause errors in care; (2) there are no outcomes data to recommend one type of handoff over another; and (3) one type of handoff cannot satisfy all types of practice, even within the same institution. Areas for future work include data-driven experimental studies that compare different techniques of handoffs and their effects on patient care.

REFERENCES

1 **Riesenberg LA**, Leitzsch J, Massucci JL, Jaeger J, Rosenfeld JC, Patow C, Padmore JS, Karpovich KP. Residents' and attending physicians' handoffs: a systematic review of the literature. *Acad Med* 2009; **84**: 1775-1787 [PMID: 19940588 DOI: 10.1097/ACM.0b013e3181bf51a6]

2 **Nagpal K**, Abboudi M, Fischler L, Schmidt T, Vats A, Manchanda C, Sevdalis N, Scheidegger D, Vincent C, Moorthy K. Evaluation of postoperative handover using a tool to assess information transfer and teamwork. *Ann Surg* 2011; **253**: 831-837 [PMID: 21475027 DOI: 10.1097/SLA.0b013e318211d849]

3 **Anwari JS**. Quality of handover to the postanaesthesia care unit nurse. *Anaesthesia* 2002; **57**: 488-493 [PMID: 12004809 DOI: 10.1046/j.0003-2409.2001.02406.x]

4 **Nasca TJ**, Day SH, Amis ES. The new recommendations on duty hours from the ACGME Task Force. *N Engl J Med* 2010; **363**: e3 [PMID: 20573917 DOI: 10.1056/NEJMsb1005800]

5 **Griffen FD**. The impact of transparency on patient safety and liability. *Bull Am Coll Surg* 2008; **93**: 19-23 [PMID: 18390226]

6 **Solet DJ**, Norvell JM, Rutan GH, Frankel RM. Lost in translation: challenges and opportunities in physician-to-physician communication during patient handoffs. *Acad Med* 2005; **80**: 1094-1099 [PMID: 16306279 DOI: 10.1097/00001888-200512000-00005]

7 **Cohen MD**, Hilligoss PB. The published literature on handoffs in hospitals: deficiencies identified in an extensive review. *Qual Saf Health Care* 2010; **19**: 493-497 [PMID: 20378628 DOI: 10.1136/qshc.2009.033480]

8 Patient safety: Essentials for health care. 5th ed. Joint Commission Resources. Oakbrook Terrace, Ill: Joint Commission Resources, 2009

9 **Sinha M**, Shriki J, Salness R, Blackburn PA. Need for standardized sign-out in the emergency department: a survey of emergency medicine residency and pediatric emergency medicine fellowship program directors. *Acad Emerg Med* 2007; **14**: 192-196 [PMID: 17192443 DOI: 10.1197/j.aem.2006.09.048]

10 **Nagpal K**, Vats A, Ahmed K, Vincent C, Moorthy K. An evaluation of information transfer through the continuum of surgical care: a feasibility study. *Ann Surg* 2010; **252**: 402-407 [PMID: 20647920 DOI: 10.1097/SLA.0b013e3181e986df]

11 **Gawande AA**, Zinner MJ, Studdert DM, Brennan TA. Analysis of errors reported by surgeons at three teaching hospitals. *Surgery* 2003; **133**: 614-621 [PMID: 12796727 DOI: 10.1067/msy.2003.169]

12 **Scoglietti VC**, Collier KT, Long EL, Bush GP, Chapman JR, Nakayama DK. After-hours complications: evaluation of the predictive accuracy of resident sign-out. *Am Surg* 2010; **76**: 682-686 [PMID: 20698370]

13 **Singh H**, Thomas EJ, Petersen LA, Studdert DM. Medical errors involving trainees: a study of closed malpractice claims from 5 insurers. *Arch Intern Med* 2007; **167**: 2030-2036 [PMID: 17954795 DOI: 10.1001/archinte.167.19.2030]

14 **Riebschleger MP**, Bohl J. New Standards for Teamwork: Discussion and Justification. In: The ACGME 2011 Duty Hour Standards: Enhancing Quality of Care, Supervision, and Resident Professional Development. Chicago, IL: Accreditation Council for Graduate Medical Education; 2011: 53-56

15 Accreditation Council for Graduate Medical Education Common Program Requirements. [accessed 2016 Jan 26]. ACGME Website. Available from: URL: http//www.acgme.org/acgmeweb/Portals/0/PFAssets/ProgramRequirements/CPRs_07012015.pdf

16 **Barden CB**, Specht MC, McCarter MD, Daly JM, Fahey TJ. Effects of limited work hours on surgical training. *J Am Coll Surg* 2002; **195**: 531-538 [PMID: 12375759 DOI: 10.1016/S1072-7515(02)01242-5]

17 **Kemp CD**, Bath JM, Berger J, Bergsman A, Ellison T, Emery K, Garonzik-Wang J, Hui-Chou HG, Mayo SC, Serrano OK, Shridharani S, Zuberi K, Lipsett PA, Freischlag JA. The top 10 list for a safe and effective sign-out. *Arch Surg* 2008; **143**: 1008-1010 [PMID: 18936381 DOI: 10.1001/archsurg.143.10.1008]

18 **Johner AM**, Merchant S, Aslani N, Planting A, Ball CG, Widder S, Pagliarello G, Parry NG, Klassen D, Hameed SM. Acute general surgery in Canada: a survey of current handover practices. *Can J Surg* 2013; **56**: E24-E28 [PMID: 23706854 DOI: 10.1503/

cjs.035011]
19 **Al-Benna S**, Al-Ajam Y, Alzoubaidi D. Burns surgery handover study: trainees' assessment of current practice in the British Isles. *Burns* 2009; **35**: 509-512 [PMID: 19297101 DOI: 10.1016/j.burns.2008.11.008]
20 **Schouten WM**, Burton MC, Jones LD, Newman J, Kashiwagi DT. Association of face-to-face handoffs and outcomes of hospitalized internal medicine patients. *J Hosp Med* 2015; **10**: 137-141 [PMID: 25736613 DOI: 10.1002/jhm.2293]
21 **Flanagan ME**, Patterson ES, Frankel RM, Doebbeling BN. Evaluation of a physician informatics tool to improve patient handoffs. *J Am Med Inform Assoc* 2009; **16**: 509-515 [PMID: 19390111 DOI: 10.1197/jamia.M2892]
22 **Parker J**, Coiera E. Improving clinical communication: a view from psychology. *J Am Med Inform Assoc* 2000; **7**: 453-461 [PMID: 10984464 DOI: 10.1136/jamia.2000.0070453]
23 **Vergales J**, Addison N, Vendittelli A, Nicholson E, Carver DJ, Stemland C, Hoke T, Gangemi J. Face-to-face handoff: improving transfer to the pediatric intensive care unit after cardiac surgery. *Am J Med Qual* 2015; **30**: 119-125 [PMID: 24443318 DOI: 10.1177/1062860613518419]
24 **Shah DR**, Galante JM, Bold RJ, Canter RJ, Martinez SR. Text messaging among residents and faculty in a university general surgery residency program: prevalence, purpose, and patient care. *J Surg Educ* 2013; **70**: 826-834 [PMID: 24209663 DOI: 10.1016/j.jsurg.2012.05.003]
25 **Zavalkoff SR**, Razack SI, Lavoie J, Dancea AB. Handover after pediatric heart surgery: a simple tool improves information exchange. *Pediatr Crit Care Med* 2011; **12**: 309-313 [PMID: 20975613 DOI: 10.1097/PCC.0b013e3181fe27b6]

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Should multi-gene panel testing replace limited BRCA1/2 testing? A review of genetic testing for hereditary breast and ovarian cancers

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Abstract

Clinical testing of patients for hereditary breast and ovarian cancer syndromes began in the mid-1990s with the identification of the *BRCA1* and *BRCA2* genes. Since then, mutations in dozens of other genes have been correlated to increased breast, ovarian, and other cancer risk. The following decades of data collection and patient advocacy allowed for improvements in medical, legal, social, and ethical advances in genetic testing. Technological advances have made it possible to sequence multiple genes at once in a panel to give patients a more thorough evaluation of their personal cancer risk. Panel testing increases the detection of mutations that lead to increased risk of breast, ovarian, and other cancers and can better guide individualized screening measures compared to limited BRCA testing alone. At the same time, multi-gene panel testing is more time-and cost-efficient. While the clinical application of panel testing is in its infancy, many problems arise such as lack of guidelines for management of newly identified gene mutations, high rates of variants of uncertain significance, and limited ability to screen for some cancers. Through on-going concerted efforts of pooled data collection and analysis, it is likely that the benefits of multi-gene panel testing will outweigh the risks in the near future.

Key words: Panel testing; Genetic testing; *BRCA*; Breast cancer

Core tip: Evaluating multiple genes in a panel test has clear advantages over BRCA1/2 testing including a greater likelihood of identifying patients with actionable pathogenic mutations, improved efficiency over sequential testing, and lower overall cost. At the same time, panel testing comes with limitations; most notably a lack of clear management guidelines for mutations in moderate penetrance genes and limited evidence-based

clinical validity. As more information is gathered on these moderate- and low-penetrance gene mutations, the ability to guide clinical decisions for patients will continue to improve.

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HISTORICAL CONTEXT

The first hereditary susceptibility gene associated with breast cancer risk was identified in 1994 and called *BRCA1*[1,2]. At that time, there were approximately 182000 cases of breast cancer diagnosed annually in the United States[3] and a growing concern to identify causative factors for a highly prevalent disease. Shortly thereafter in 1995, the *BRCA2* gene was identified and these two genes, *BRCA1* and *BRCA2* (*BRCA1/2*), began to play an important role in evaluating newly diagnosed breast cancer patients and others with high-risk family histories.

Initially, when clinical testing of *BRCA1/2* mutations began in 1996, there were many uncertainties and criticisms: Data to demonstrate outcomes and benefit of proposed management was still being gathered, directive guidelines did not exist, and understanding of the expanding phenotype and variable penetrance was still occurring. The rate of inconclusive results was higher, time to receive results was closer to two months, patient concern about genetic discrimination was much more pronounced, and protective legislation specific to genetic test results was limited. Furthermore, the long-term psychological impact of genetic testing results was yet unknown.

It is now well-documented that germline *BRCA1/2* mutations significantly increase risk for breast, ovarian, and male breast cancer as well as moderately increase risk for prostate and pancreatic cancer[4-6]. Established national guidelines identify which clinical histories warrant *BRCA1/2* genetic testing and how to manage patients who carry *BRCA1/2* mutations, specifically high-risk surveillance and risk-reducing surgical options[7]. *BRCA1/2* genetic testing is now routinely covered by insurance companies in patients with defined clinical histories, the rate of inconclusive results is less than 5%, and results are returned in approximately two weeks. Ultimately, a federal law was passed called Genetic Information Nondiscrimination Act "GINA" of 2008 to prevent medical insurance companies and employers from discriminating against individuals on the basis of their genetic information[8]. Fortunately, initial data has shown that no significant long-term psychological and emotional consequences occur as a result of genetic testing[9].

Many breast surgeons incorporate *BRCA1/2* testing into the initial work-up of newly diagnosed breast cancer patients who meet testing criteria to guide surgical decisions. Family members of affected individuals or other high-risk patients can also be easily referred for cancer genetic counseling for testing and preventive intervention strategies. The high prevalence of *BRCA1/2* mutations among male breast cancer patients and ovarian cancer patients has led to recommendations that any patient with one of these diseases obtain *BRCA1/2* testing[7]. In the last few years, testing criteria have also expanded to include pancreatic cancer and high-grade prostate cancer indications[7].

RECENT SHIFTS

Of hereditary breast cancers, only 30%-50% is attributed to mutations in *BRCA1* and *BRCA2* genes[10-12]. Over several decades of research, additional genetic mutations in numerous other genes have been implicated in breast and ovarian cancer risk. There are now over 20 genes and hundreds of mutations that have been implicated in the development of breast and/or ovarian cancer (Table 1)[12-14].

Traditionally, testing patients or those at risk for hereditary breast and ovarian cancer risk-began with evaluating *BRCA1/2*. If results were negative, additional testing was offered, often several weeks to months later, only if the patient met certain criteria for additional genetic syndromes. Numerous advances from scientific technology to legislation to public awareness and media, have shifted this testing paradigm.

Technological advances in DNA sequencing have come to what some have termed a "tipping point" in the advancement of genetic evaluation and discovery of new mutations related to hereditary cancer risk[15]. In place of more tedious methods of DNA sequencing using Sanger sequencing techniques, massively parallel DNA sequencing using Next Generation Sequencing (NGS) allows multiple genes to be evaluated at once.

With NGS, came the opportunity to offer panel testing, or evaluating numerous genes at once rather than in sequence. Panel testing decreased the turn-over-time for results while minimizing the cost of the test[10,13]. Even with panel testing, however, there were still restrictions with including *BRCA1/2* testing on a panel due to patents held by the founding company on evaluating these genes for almost 20 years. It was not until a 2013 Supreme Court ruling of Association for Molecular Pathology v. Myriad Genetics that many of these patents that restricted *BRCA1/2* testing became invalidated[16]. Since then, multi-gene panels offered by numerous genetic testing companies were able to include *BRCA1/2* in their panels and offer patients comprehensive testing upfront[17].

Another equally important event that occurred to influence hereditary genetic testing patterns was the public disclosure of the highly acclaimed actress Angelina

Table 1 List of select genes that can be found on multi-gene panels and associated cancer risks

Gene	Cancer risk[1]
ATM	Breast, pancreatic cancer
BARD1	Breast
BRCA1	Breast, ovarian, male breast cancer, melanoma, pancreatic cancer
BRCA2	Breast, ovarian, male breast cancer, melanoma, pancreatic, prostate cancer
BRIP1	Breast
CDH1	Breast, diffuse-type gastric cancer
CHEK2	Breast, colon, ovarian
EPCAM	Colorectal, uterine, stomach, ovarian
MLH1	Colorectal, uterine, stomach, ovarian
MRE11A	Breast
MSH2	Colorectal, uterine, ovarian
MSH6	Colorectal, uterine, stomach, ovarian
MUTYH	Breast, colorectal, other gastrointestinal sites
NBN	Breast
NF1	Breast, peripheral nerve sheath tumors, gliomas, leukemias, pheochromocytomas
PALB2	Breast, pancreatic cancer
PMS2	Colorectal, uterine, stomach, ovarian
PTEN	Breast, thyroid, endometrial cancer
RAD50	Breast
RAD51C	Breast, ovarian
RAD51D	Breast, ovarian
STK11	Breast, gastrointestinal, ovarian
TP53	Breast, ovarian, osteosarcomas, brain tumors, colorectal, other gastrointestinal sites

[1]List of cancer sites is not all-inclusive as additional sites may be pending further clinical validation.

Jolie's *BRCA1* mutation status in 2013. When Jolie explained her decision to choose prophylactic bilateral mastectomy and oophorectomy due to her *BRCA1* mutation, mainstream media brought public awareness to the importance of hereditary genetic testing and as a result, there became a surge in numbers of patients undergoing testing[18]. While numbers referred for testing have more than doubled in some locations, the majority of referrals have been found to be appropriate and for qualified candidates[18].

NEWER DATA

With this shift in testing, the clinical impact of multi-gene panel testing has become apparent. Prior to inclusion of *BRCA1/2* in panels, LaDuca *et al*[19] evaluated over 2000 patients who underwent multi-gene panel testing with 14-21 genes (excluding *BRCA1/2*) between March 2012 and May 2013. Overall, 8.3% of patients were found to carry pathogenic mutations, ranging from 7.2%-9.6% depending on the number of genes evaluated. Of patients who were deemed to be high risk for hereditary breast and ovarian cancer and underwent a "breast" panel with genes implicated in breast cancer pathogenesis, 10.9% of patients were found to carry pathogenic mutations. The genes found to be mutated most frequently in this cohort of high-risk patients included *PALB2*, *CHEK2*, and *ATM*.

Similarly, Tung *et al*[20] evaluated over 2000 high-risk patients who underwent a NGS multi-gene panel testing with 25 genes including *BRCA1/2*. Of patients who underwent panel testing with *BRCA1/2*, 9.3% were found to carry a *BRCA1/2* mutation and an additional 4.2% of patients carried non-*BRCA* mutations again with the most frequent gene mutations in *PALB2*, *CHEK2*, and *ATM*. Smaller studies have also shown the benefit of panel testing[14,21-23].

We have demonstrated that multi-gene panel testing nearly doubles the pathogenic mutation detection rate in patients with increased risk of hereditary breast and/or ovarian cancer when compared to limited *BRCA1/2* testing alone in a cohort of 966 high-risk patients[21]. Likewise, a French group used their own NGS panel of 27 genes to evaluate 708 high-risk patients and found a 15.4% mutation detection rate[14]. Mutations in *BRCA1/2* accounted for 59% of these genetic alterations in the French study, while 41% were non-*BRCA* genes, again most frequently in *PALB2*, *CHEK2*, and *ATM* genes.

When patients undergo panel testing with multiple genes, there is an increased detection of pathogenic mutations, but there is also increased detection of DNA variants of uncertain significance (VUS). Depending on the number of genes in a panel and the patients who are tested, VUS rates from panel testing have been reported to range from 6.7%-41.7%[19-21]. The VUS rate for any given gene will be highest initially as data starts to accumulate, then will decrease over time[19]. Nonetheless, *BRCA1/2* testing is still associated with a VUS rate of approximately 4%[21].

BENEFITS

In order for a new testing method to replace an es-

tablished algorithm, a substantial benefit should be possible with limited consequences. There are a number of obvious advantages of multi-gene panel testing over limited *BRCA1/2* testing. Panel testing not only provides patients with more information about their hereditary risk by increasing the detection of pathogenic mutations, but it also identifies actionable mutations for which patients can choose to increase surveillance of high risk cancers, initiate chemoprevention, or even undergo prophylactic surgery to remove a potential at-risk organ site.

Carrying a *BRCA1/2* mutation leads to a lifetime risk of breast cancer up to 85% and a lifetime risk of developing ovarian cancer between 15%-60%[4-6]. Increased surveillance with breast MRI can detect breast cancers at earliest stages for these patients, while prophylactic bilateral mastectomy decreases this risk by over 90% and prophylactic bilateral salpingo-oophorectomy minimizes the risk of both ovarian and breast cancer[24,25]. Similarly, patients with mutations in non-*BRCA* genes that are associated with increased risk of breast cancer, such as *PALB2*, *CHEK2*, and *ATM*, may also benefit from increased screening with breast MRI. Other patients with these non-*BRCA* gene mutations, especially those with a strong family history of breast cancer or who carry particularly penetrant gene mutations may even benefit from prophylactic mastectomies[26-31].

In addition to identifying genes associated with breast and/or ovarian cancer risk, panel testing identifies genes with cancer risk in other organ sites (Table 1). Mutations in the *PTEN* gene, for example, confer a risk of breast, thyroid, and endometrial cancer. Patients with *PTEN* mutations and the related Cowden syndrome are recommended to not only have increased breast cancer surveillance, but annual thyroid ultrasounds and endometrial evaluations as well[7]. On the other hand, *MSH2* mutations are implicated in Lynch syndrome, which is characterized by increased risk of early onset colon, uterine, and ovarian cancers[32]. For these patients, consideration of hysterectomy and oophorectomy and increased frequency of colonoscopies should be included in counseling. Multi-gene panel testing can help direct focused screening in high risk patients and even enable risk-reducing interventions.

Other benefits of panel testing over sequential testing include the ability to test for genes that a patient might not normally be considered for. This is especially true for more rare gene mutations that are typically associated with particular family inheritance patterns or traits such as Li Fraumeni syndrome or Cowden Syndrome[33,34]. With panel testing, these rare mutation carriers can be more readily identified in patients with limited or unknown family history.

Fortunately, NGS allows for multi-gene panel testing to be both efficient and cost-effective[13,23,35]. Rather than thousands of dollars for only *BRCA1/2* testing, dozens of genes can now be sequenced at once for a fraction of the cost.

LIMITATIONS AND CONCERNS

While panel testing increases the diagnostic yield by up to 50% compared to *BRCA1/2* testing alone, sometimes the pathogenic mutation identified is in a gene for which there is limited data as to the cancer risks and cancer spectrum so patient management recommendations will not be available. National Comprehensive Cancer Network guidelines currently provide detailed recommendations for a handful of well-characterized, highly-penetrant genes (*BRCA1, BRCA2, PTEN, TP53, CDH1,* and *STK11*) and also provide breast and ovarian management considerations for some of the genes commonly identified by panel testing (*ATM, CHEK2*, and *PALB2*)[7]. Detailed recommendations, however, accounting for the other cancer risks associated with these genes and recommendations for management of patients with mutations in less-characterized genes do not yet exist. It is also possible that mutations in moderate/intermediate-risk genes may not entirely explain a personal and/or family history of cancer; the role of gene/gene and gene/environment interactions could influence the manifestation of a gene mutation and/or cause phenocopies in the family (people who do not carry a known familial mutation but develop a cancer associated with the familial gene mutation). In addition, others have argued that there is a lack of clinical validity due to limited data sets that estimate cancer risk for many of the genes found on panels[36]. Clearly larger population and family-based studies will be needed to provide the best risk-estimates for appropriate counseling for the more rare gene mutations. Given this, management recommendations for patients (and their family members) with mutations in less-characterized genes need to take into account what is known about the specific gene as well as the personal and family clinical history[21].

With the identification of cancer risk outside of breast, colon, and ovarian cancer, comes the question of how to screen for and/or prevent rare cancers that associated with specific gene mutations (Table 1). This dilemma is not specific to the "newer" genes included on many panels. Patients with a *BRCA1/2* gene mutation and family history of pancreatic cancer are counseled that they likely have an increased risk for pancreatic cancer, but screening for early-detection of pancreatic cancer is not well-established and only recommended within the scope of a clinical trial[37]. Patients found to carry a *TP53* gene mutation are informed that they have a significantly elevated risk for multiple types of cancers, some of which we have screening modalities and guidelines for but others which do not[7]. On the other hand, patients with a *CDH1* gene mutation can have up to a 70% risk of gastric cancer by age 80 and may be recommended to consider prophylactic total gastrectomy[38]. As with targeted *BRCA1/2* or *TP53* testing, patients undergoing panel testing need to be informed of the benefits, limitations, and possible implications of testing, including limited screening and

prevention options for certain cancers.

Another limitation with panel testing is the higher rate of inconclusive (variant of uncertain significance) results. Similar to the early days of *BRCA1/2* genetic testing when VUS rates were higher, clinicians ordering panels for their patients must be aware of the higher possibility of identifying a VUS and make empiric management recommendations based on the personal and family clinical history when such a result is received[19-22]. An inconclusive result can cause patient (and clinician) anxiety about future cancer risks and potential risk for family members. Patients with VUS results can contribute to research specific to their gene variant and participate in national registries such as the Prospective Registry of Multiplex Testing. Often, however, facilitation of patient participation in such research falls to the managing busy clinician. As additional data is accumulated, VUS results are ultimately re-classified to either benign or deleterious, often years later, and the original ordering clinician receives the reclassification report that they must then act upon.

Lastly, as with any emerging technology, NGS and multi-gene panel tests are currently without established insurance guidelines for payment reimbursement. Without a panel-specific current procedural terminology (CPT) code, billing for panel tests is not as straightforward as *BRCA1/2* or Lynch testing for which gene-specific CPT codes exist. Obtaining authorization for *BRCA1/2* testing is fairly simple, while obtaining authorization for panel testing may require more work from the clinicians' office, although some laboratories will perform insurance authorization services to support the process.

CONCLUSION

Evaluating patients at risk for hereditary breast and ovarian cancer syndromes has transformed in a short period of time. Mutations in *BRCA1/2* genes are still the most common gene mutations accounting for inherited cancer risk, however numerous other genes have been added to the spectrum of hereditary cancer risk. Evaluating multiple genes in a panel test has clear advantages over *BRCA1/2* testing including a greater likelihood of identifying patients with actionable pathogenic mutations, improved efficiency over sequential testing, and lower overall cost. At the same time, panel testing comes with limitations; most notably a lack of clear management guidelines for mutations in moderate penetrance genes and limited evidence-based clinical validity. As more information is gathered on these moderate- and low-penetrance gene mutations and VUS through national efforts, our ability to guide clinical decisions for our patients will continue to improve. In the interim, thoughtful application of existing guidelines for gene mutations with cancer risk profiles similar to genes with established guidelines can be applied in the management of patients with mutations in some of these newer genes.

REFERENCES

1 **Miki Y**, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S, Liu Q, Cochran C, Bennett LM, Ding W. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. *Science* 1994; **266**: 66-71 [PMID: 7545954 DOI: 10.1126/science.7545954]

2 **Friedman LS**, Ostermeyer EA, Szabo CI, Dowd P, Lynch ED, Rowell SE, King MC. Confirmation of BRCA1 by analysis of germline mutations linked to breast and ovarian cancer in ten families. *Nat Genet* 1994; **8**: 399-404 [PMID: 7894493 DOI: 10.1038/ng1294-399]

3 **SEER cancer statistics review 1973-1994.** [accessed 2015 Aug 8]. Available from: URL: http: //seer.cancer.gov/archive/csr/1973_1994/overview.pdf

4 **Struewing JP**, Hartge P, Wacholder S, Baker SM, Berlin M, McAdams M, Timmerman MM, Brody LC, Tucker MA. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. *N Engl J Med* 1997; **336**: 1401-1408 [PMID: 9145676 DOI: 10.1056/NEJM199705153362001]

5 **Antoniou A**, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, Loman N, Olsson H, Johannsson O, Borg A, Pasini B, Radice P, Manoukian S, Eccles DM, Tang N, Olah E, Anton-Culver H, Warner E, Lubinski J, Gronwald J, Gorski B, Tulinius H, Thorlacius S, Eerola H, Nevanlinna H, Syrjäkoski K, Kallioniemi OP, Thompson D, Evans C, Peto J, Lalloo F, Evans DG, Easton DF. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet* 2003; **72**: 1117-1130 [PMID: 12677558 DOI: 10.1086/375033]

6 **Ford D**, Easton DF, Bishop DT, Narod SA, Goldgar DE. Risks of cancer in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. *Lancet* 1994; **343**: 692-695 [PMID: 7907678 DOI: 10.1016/S0140-6736(94)91578-4]

7 **National Comprehensive Cancer Network.** Genetic/Familial High-Risk Assessment: Breast and Ovarian. NCCN Clinical Practice Guidelines in Oncology. [accessed 2015 Aug 15]. Available from: URL: http://www.nccn.org/professionas/physician_gls/pdf/genetics_screening.pdf

8 **Genetic Information Nondiscrimination Act of 2008.** Available from: URL: http://www.eeoc.gov/laws/statutes/gina.cfm

9 **Lerman C**, Narod S, Schulman K, Hughes C, Gomez-Caminero A, Bonney G, Gold K, Trock B, Main D, Lynch J, Fulmore C, Snyder C, Lemon SJ, Conway T, Tonin P, Lenoir G, Lynch H. BRCA1 testing in families with hereditary breast-ovarian cancer. A prospective study of patient decision making and outcomes. *JAMA* 1996; **275**: 1885-1892 [PMID: 8648868 DOI: 10.1001/jama.1996.03530480027036]

10 **Walsh T**, King MC. Ten genes for inherited breast cancer. *Cancer Cell* 2007; **11**: 103-105 [PMID: 17292821 DOI: 10.1016/j.ccr.2007.01.010]

11 **van der Groep P**, van der Wall E, van Diest PJ. Pathology of hereditary breast cancer. *Cell Oncol* (Dordr) 2011; **34**: 71-88 [PMID: 21336636 DOI: 10.1007/s13402-011-0010-3]

12 **Meindl A**, Ditsch N, Kast K, Rhiem K, Schmutzler RK. Hereditary breast and ovarian cancer: new genes, new treatments, new concepts. *Dtsch Arztebl Int* 2011; **108**: 323-330 [PMID: 21637635 DOI: 10.3238/arztebl.2011.0323]

13 **Walsh T**, Lee MK, Casadei S, Thornton AM, Stray SM, Pennil C, Nord AS, Mandell JB, Swisher EM, King MC. Detection of inherited mutations for breast and ovarian cancer using genomic capture and massively parallel sequencing. *Proc Natl Acad Sci USA* 2010; **107**: 12629-12633 [PMID: 20616022 DOI: 10.1073/pnas.1007983107]

14 **Castéra L**, Krieger S, Rousselin A, Legros A, Baumann JJ, Bruet O, Brault B, Fouillet R, Goardon N, Letac O, Baert-Desurmont S, Tinat J, Bera O, Dugast C, Berthet P, Polycarpe F, Layet V, Hardouin A, Frébourg T, Vaur D. Next-generation sequencing for the diagnosis of hereditary breast and ovarian cancer using genomic capture targeting multiple candidate genes. *Eur J Hum Genet* 2014; **22**: 1305-1313 [PMID: 24549055 DOI: 10.1038/ejhg.2014.16]

15 **Rainville IR**, Rana HQ. Next-generation sequencing for inherited breast cancer risk: counseling through the complexity. *Curr Oncol Rep* 2014; **16**: 371 [PMID: 24488544 DOI: 10.1007/s11912-013-0371-z]

16 **Association for Molecular Pathology *v.* Myriad Genetics.** Available from: URL: https://www.oyez.org/cases/2012/12-398

17 **Azvolinsky A**. Supreme Court ruling broadens BRCA testing options. *J Natl Cancer Inst* 2013; **105**: 1671-1672 [PMID: 24198329 DOI: 10.1093/jnci/djt342]

18 **Evans DG**, Barwell J, Eccles DM, Collins A, Izatt L, Jacobs C, Donaldson A, Brady AF, Cuthbert A, Harrison R, Thomas S, Howell A, Miedzybrodzka Z, Murray A. The Angelina Jolie effect: how high celebrity profile can have a major impact on provision of cancer related services. *Breast Cancer Res* 2014; **16**: 442 [PMID: 25510853 DOI: 10.1186/s13058-014-0442-6]

19 **LaDuca H**, Stuenkel AJ, Dolinsky JS, Keiles S, Tandy S, Pesaran T, Chen E, Gau CL, Palmaer E, Shoaepour K, Shah D, Speare V, Gandomi S, Chao E. Utilization of multigene panels in hereditary cancer predisposition testing: analysis of more than 2,000 patients. *Genet Med* 2014; **16**: 830-837 [PMID: 24763289 DOI: 10.1038/gim.2014.40]

20 **Tung N**, Battelli C, Allen B, Kaldate R, Bhatnagar S, Bowles K, Timms K, Garber JE, Herold C, Ellisen L, Krejdovsky J, DeLeonardis K, Sedgwick K, Soltis K, Roa B, Wenstrup RJ, Hartman AR. Frequency of mutations in individuals with breast cancer referred for BRCA1 and BRCA2 testing using next-generation sequencing with a 25-gene panel. *Cancer* 2015; **121**: 25-33 [PMID: 25186627 DOI: 10.1002/cncr.29010]

21 **Kapoor NS**, Curcio LD, Blakemore CA, Bremner AK, McFarland RE, West JG, Banks KC. Multigene Panel Testing Detects Equal Rates of Pathogenic BRCA1/2 Mutations and has a Higher Diagnostic Yield Compared to Limited BRCA1/2 Analysis Alone in Patients at Risk for Hereditary Breast Cancer. *Ann Surg Oncol* 2015; **22**: 3282-3288 [PMID: 26219241 DOI: 10.1245/s10434-015-4754-2]

22 **Kurian AW**, Hare EE, Mills MA, Kingham KE, McPherson L, Whittemore AS, McGuire V, Ladabaum U, Kobayashi Y, Lincoln SE, Cargill M, Ford JM. Clinical evaluation of a multiple-gene sequencing panel for hereditary cancer risk assessment. *J Clin Oncol* 2014; **32**: 2001-2009 [PMID: 24733792 DOI: 10.1200/JCO.2013.53.6607]

23 **Yorczyk A**, Robinson LS, Ross TS. Use of panel tests in place of single gene tests in the cancer genetics clinic. *Clin Genet* 2015; **88**: 278-282 [PMID: 25318351 DOI: 10.1111/cge.12488]

24 **Heemskerk-Gerritsen BA**, Brekelmans CT, Menke-Pluymers MB, van Geel AN, Tilanus-Linthorst MM, Bartels CC, Tan M, Meijers-Heijboer HE, Klijn JG, Seynaeve C. Prophylactic mastectomy in BRCA1/2 mutation carriers and women at risk of hereditary breast cancer: long-term experiences at the Rotterdam Family Cancer Clinic. *Ann Surg Oncol* 2007; **14**: 3335-3344 [PMID: 17541692 DOI: 10.1245/s10434-007-9449-x]

25 **Domchek SM**, Friebel TM, Singer CF, Evans DG, Lynch HT, Isaacs C, Garber JE, Neuhausen SL, Matloff E, Eeles R, Pichert G, Van t'veer L, Tung N, Weitzel JN, Couch FJ, Rubinstein WS, Ganz PA, Daly MB, Olopade OI, Tomlinson G, Schildkraut J, Blum JL, Rebbeck TR. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. *JAMA* 2010; **304**: 967-975 [PMID: 20810374 DOI: 10.1001/jama.2010.1237]

26 **Tischkowitz M**, Xia B, Sabbaghian N, Reis-Filho JS, Hamel N, Li G, van Beers EH, Li L, Khalil T, Quenneville LA, Omeroglu A, Poll A, Lepage P, Wong N, Nederlof PM, Ashworth A, Tonin PN, Narod SA, Livingston DM, Foulkes WD. Analysis of PALB2/FANCN-associated breast cancer families. *Proc Natl Acad Sci USA* 2007; **104**: 6788-6793 [PMID: 17420451 DOI: 10.1073/pnas.0701724104]

27 **Rahman N**, Seal S, Thompson D, Kelly P, Renwick A, Elliott A, Reid S, Spanova K, Barfoot R, Chagtai T, Jayatilake H, McGuffog L, Hanks S, Evans DG, Eccles D, Easton DF, Stratton MR. PALB2, which encodes a BRCA2-interacting protein, is a breast cancer susceptibility gene. *Nat Genet* 2007; **39**: 165-167 [PMID: 17200668 DOI: 10.1038/ng1959]

28 **Antoniou AC**, Casadei S, Heikkinen T, Barrowdale D, Pylkäs K, Roberts J, Lee A, Subramanian D, De Leeneer K, Fostira F, Tomiak E, Neuhausen SL, Teo ZL, Khan S, Aittomäki K, Moilanen JS, Turnbull C, Seal S, Mannermaa A, Kallioniemi A, Lindeman GJ, Buys SS, Andrulis IL, Radice P, Tondini C, Manoukian S, Toland AE, Miron P, Weitzel JN, Domchek SM, Poppe B, Claes KB, Yannoukakos D, Concannon P, Bernstein JL, James PA, Easton DF, Goldgar DE, Hopper JL, Rahman N, Peterlongo P, Nevanlinna H, King MC, Couch FJ, Southey MC, Winqvist R, Foulkes WD, Tischkowitz M. Breast-cancer risk in families with mutations in PALB2. *N Engl J Med* 2014; **371**: 497-506 [PMID: 25099575 DOI: 10.1056/NEJMoa1400382]

29 **Chenevix-Trench G**, Spurdle AB, Gatei M, Kelly H, Marsh A, Chen X, Donn K, Cummings M, Nyholt D, Jenkins MA, Scott C, Pupo GM, Dörk T, Bendix R, Kirk J, Tucker K, McCredie MR, Hopper JL, Sambrook J, Mann GJ, Khanna KK. Dominant negative ATM mutations in breast cancer families. *J Natl Cancer Inst* 2002; **94**: 205-215 [PMID: 11830610 DOI: 10.1093/jnci/94.3.205]

30 **Goldgar DE**, Healey S, Dowty JG, Da Silva L, Chen X, Spurdle AB, Terry MB, Daly MJ, Buys SM, Southey MC, Andrulis I, John EM, Khanna KK, Hopper JL, Oefner PJ, Lakhani S, Chenevix-Trench G. Rare variants in the ATM gene and risk of breast cancer. *Breast Cancer Res* 2011; **13**: R73 [PMID: 21787400 DOI: 10.1186/bcr2919]

31 **Thompson D**, Duedal S, Kirner J, McGuffog L, Last J, Reiman A, Byrd P, Taylor M, Easton DF. Cancer risks and mortality in heterozygous ATM mutation carriers. *J Natl Cancer Inst* 2005; **97**: 813-822 [PMID: 15928302 DOI: 10.1093/jnci/dji141]

32 **NCCN Clinical Practice Guidelines in Oncology.** Genetic/Familial High-Risk Assessment: Colorectal Version 2.2014. [accessed 2015 Aug 15]. Available from: URL: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp

33 **Li FP**, Fraumeni JF, Mulvihill JJ, Blattner WA, Dreyfus MG, Tucker MA, Miller RW. A cancer family syndrome in twenty-four kindreds. *Cancer Res* 1988; **48**: 5358-5362 [PMID: 3409256]

34 **Lindor NM**, McMaster ML, Lindor CJ, Greene MH. Concise handbook of familial cancer susceptibility syndromes - second edition. *J Natl Cancer Inst Monogr* 2008; **(38)**: 1-93 [PMID: 18559331 DOI: 10.1093/jncimonographs/lgn001]

35 **Domchek SM**, Bradbury A, Garber JE, Offit K, Robson ME. Multiplex genetic testing for cancer susceptibility: out on the high wire without a net? *J Clin Oncol* 2013; **31**: 1267-1270 [PMID: 23460708 DOI: 10.1200/JCO.2012.46.9403]

36 **Easton DF**, Pharoah PD, Antoniou AC, Tischkowitz M, Tavtigian SV, Nathanson KL, Devilee P, Meindl A, Couch FJ, Southey M, Goldgar DE, Evans DG, Chenevix-Trench G, Rahman N, Robson M, Domchek SM, Foulkes WD. Gene-panel sequencing and the prediction of breast-cancer risk. *N Engl J Med* 2015; **372**: 2243-2257 [PMID: 26014596 DOI: 10.1056/NEJMsr1501341]

37 **Iqbal J**, Ragone A, Lubinski J, Lynch HT, Moller P, Ghadirian P, Foulkes WD, Armel S, Eisen A, Neuhausen SL, Senter L, Singer CF, Ainsworth P, Kim-Sing C, Tung N, Friedman E, Llacuachaqui M, Ping S, Narod SA. The incidence of pancreatic cancer in BRCA1 and BRCA2 mutation carriers. *Br J Cancer* 2012; **107**: 2005-2009 [PMID: 23099806 DOI: 10.1038/bjc.2012.483]

38 **Hansford S**, Kaurah P, Li-Chang H, Woo M, Senz J, Pinheiro H, Schrader KA, Schaeffer DF, Shumansky K, Zogopoulos G, Santos TA, Claro I, Carvalho J, Nielsen C, Padilla S, Lum A, Talhouk A, Baker-Lange K, Richardson S, Lewis I, Lindor NM, Pennell E, MacMillan A, Fernandez B, Keller G, Lynch H, Shah SP, Guilford P, Gallinger S, Corso G, Roviello F, Caldas C, Oliveira C, Pharoah PD, Huntsman DG. Hereditary Diffuse Gastric Cancer Syndrome: CDH1 Mutations and Beyond. *JAMA Oncol* 2015; **1**: 23-32 [PMID: 26182300 DOI: 10.1001/jamaoncol.2014.168]

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