

Reply to the comments provided by RedPath Integrated Pathology, Inc, and to the comments sent by the public.

RedPath Integrated Pathology, Inc submitted a 49-page document with comments on the Technology Assessment. Below is a summary of the points made in that document. The document contained detailed description of several studies published as abstracts or in full text and were not included in the Technology Assessment (TA). Tufts EPC reviewed the citations and included 2 that were published after the TA was completed (and an additional one in an Addendum, see below). Reasons for exclusion of the remaining studies are provided in the corresponding Appendix. The bold font is the perceived essence of the comments. Below is the reply by the EPC.

PathfinderTG® is a platform, not a single test.

The TA examined whether there is evidence that the management of patients with topographic LOH-based genotyping is beneficial for patients, as explained in the eligibility criteria. As detailed in the Methods Section, the TA was specifically interested in studies that evaluate the clinical validity and utility of the “whole platform”. Inevitably, operational definitions of what constitutes topographic genotyping with PathfinderTG® were set. The important components are the targeted selection of microscopic-size samples and performance of LOH-based molecular analyses on said slides.

The foundational scientific concepts of PathfinderTG® are solid.

We do not examine this question. The TA examines evidence on whether the addition of topographic genotyping with (PathfinderTG®) to the usual patient management strategies is beneficial (please refer to the methods section for details).

The foundational technologies of PathfinderTG® are solid.

This is Key Question 2. The TA summarized the eligible literature, and found no studies that describe such analyses. In all fairness, this is common for many diagnostic technologies, especially lab-based ones. However, the TA did not dispute the technologies on which PathfinderTG® is based.

The TA missed recent publications. There are relevant publications not published by Dr Finkelstein.

We reviewed the suggested publications and accepted 2 additional ones that fulfill the eligibility criteria. We rephrase the description of the eligibility criteria in the Methods section to enhance clarity (they are now shown as a numbered list). The decision to focus on literature published by Dr Finkelstein was taken after personal communication with the company, where it was clarified that all relevant publications will be coauthored by him. It was deemed at the teleconference and later that this is an operational criterion.

Nevertheless, we described in an Addendum an additional publication (Shen et al 2009) that mentioned using PathfinderTG®, without having Dr Finkelstein among the authors.

There are 21 suggested publications.

As mentioned in the replies above, we included 2 papers coauthored by Dr Finkelstein and another paper in an addendum. Please, refer to the Methods Section for a description of the eligibility criteria.

NO-TG: VIOLATION OF INCLUSION CRITERION #1OR 2

M-C: VIOLATION OF ELIGIBILITY CRITERION #2 OR FULFILLING THE EXCLUSION CRITERION

N<10: VIOLATION OF ELIGIBILITY CRITERION #3

1. Schwartz M, Dvorchik I, Roayaie S, Fiel MI, Finkelstein S, Marsh JW, Martignetti JA, Llovet JM. Liver transplantation for hepatocellular carcinoma: extension of indications based on molecular markers. J Hepatol. 2008 Oct;49(4):581-8. Epub 2008 May 20.	INCLUDED
2. Khalid A, Zahid M, Finkelstein SD, Leblanc JK, Kaushik N, Ahmad N, Brugge WR, Edmundowicz SA, Hawes RH, McGrath KM. Pancreatic cyst fluid DNA analysis in evaluating pancreatic cysts: a report of the PANDA study. Gastrointest Endosc. 2009 In Press. E-published Jan 17, 2009.	EXCLUDED – NO TG
3. Khalid A, McGrath KM, Zahid M, Wilson M, Brody D, Swalsky P, Moser AJ, Lee KK, Slivka A, Whitcomb DC, Finkelstein S. The role of pancreatic cyst fluid molecular analysis in predicting cyst pathology. Clinical Gastroenterology & Hepatology. 3(10):967-73, 2005.	EXCLUDED – NO TG
4. Kowalski LD, Kanbour AI, Price FV, Finkelstein SD, Christopherson WA, Seski JC, Naus GJ, Burnham JA, Kanbour-Shakir A, Edwards RP. A case-matched molecular comparison of extraovarian versus primary ovarian adenocarcinoma. Cancer. 79(8):1587-94, 1997 Apr 15.	EXCLUDED – NO LOH – ANALYSES IN N=9
5. Ohori NP, Fowler MH, Swalsky PA, Pal R, Thompson J, Finkelstein SD. Comparative molecular analysis of loss of heterozygosity in adenocarcinoma in bile duct brushings and corresponding surgical pathology specimens. Cancer. 2003 Dec 25;99(6):379-84.	EXCLUDED N=8
6. Mohan D, Finkelstein SD, Swalsky PA, Sasatomi E, Wiley C, Hamilton RL, Lieberman F, Couce ME. Microdissection genotyping of gliomas: therapeutic and prognostic considerations. Modern Pathology. 17(11):1346-58, 2004 Nov.	EXCLUDED M-C (NO SINGLE TEST DISPOSITION PER PT)
7. Ribeiro U, Safatle-Ribeiro AV, Posner MC, Rosendale B, Bakker A, Swalsky PA, Kim R, Reynolds JC, Finkelstein SD. Comparative p53 mutational analysis of multiple primary cancers of the upper aerodigestive tract. Surgery.	EXCLUDED NO-LOH M-C

120(1):45-53, 1996 Jul.	
8. Kanbour-Shakir A, Kounelis S, Papadaki H, Price F, Edwards RP, Kelley JL, Raptis S, Bakker A, Swalsky PA, Finkelstein SD. Relationship of p53 Genotype to Second Look Recurrence and Survival in Ovarian Epithelial Malignancy. <i>Molecular Diagnosis</i> . 1:121-129, 1996.	EXCLUDED NO LOH
9. Ribeiro U Jr., Finkelstein SD, Safatle-Ribeiro AV, Landreneau RJ, Clarke MR, Bakker A, Swalsky PA, Gooding WE, Posner MC. p53 sequence analysis predicts treatment response and outcome of patients with esophageal carcinoma. <i>Cancer</i> . 83(1):7-18, 1998 Jul 1.	EXCLUDED NO-LOH M-C
10. Pollack IF, Finkelstein SD, Burnham J, Holmes EJ, Hamilton RL, Yates AJ, Finlay JL, Sposto R; Children's Cancer Group. Age and TP53 mutation frequency in childhood malignant gliomas: results in a multi-institutional cohort. <i>Cancer Research</i> . 61(20):7404-7, 2001 Oct 15.	EXCLUDED NO-LOH M-C
11. Pollack IF, Hamilton RL, James CD, Finkelstein SD, Burnham J, Yates AJ, Holmes EJ, Zhou T, Finlay JL; Children's Oncology Group. Rarity of PTEN deletions and EGFR amplification in malignant gliomas of childhood: results from the Children's Cancer Group 945 cohort. <i>J Neurosurg</i> . 2006 Nov;105(5 Suppl):418-24.	EXCLUDED M-C
12. Saad RS, Denning KL, Finkelstein SD, Liu Y, Pereira TC, Lin X, Silverman JF. Diagnostic and Prognostic Utility of Molecular Markers in Synchronous Bilateral Breast Carcinoma. <i>Mod Pathol</i> . 2008 In press.	EXCLUDED M-C
13. Lee JY, Finkelstein S, Hamilton RL, Rekha R, King JT Jr., Omalu B. Loss of heterozygosity analysis of benign, atypical, and anaplastic meningiomas. <i>Neurosurgery</i> . 55(5):1163-73, 2004.	EXCLUDED M-C
14. Finkelstein SD, Sayegh R, Bakker A, Swalsky P. Determination of tumor aggressiveness in colorectal cancer by K-ras-2 analysis. <i>Archives of Surgery</i> . 128(5):526-31; discussion 531-2, 1993 May.	EXCLUDED IN DRAFT REPORT – SEE APPENDIX
15. Finkelstein SD, Przygodzki RM, Pricolo VE, Sakallah SA, Swalsky PA, Bakker A, Lanning R, Bland KI, Cooper DL. Prediction of Biological Aggressiveness in Colorectal Cancer by p53/Kras-2 Topographic Genotyping. <i>Molecular Diagnosis</i> . 1: 5-28, 1996.	EXCLUDED NO LOH
16. Shen J, Brugge WR, DiMaio CJ, Pitman MB. Molecular analysis of Pancreatic Cyst Fluid. <i>Cancer Cytopathology</i> . 2009 In press.	“INCLUDED” IN ADDENDUM
17. Lapkus O, Gologan O, Liu Y, Swalsky PA, Wilson MM, Finkelstein SD, Silverman JF. Determination of sequential mutation accumulation in pancreas and bile duct brushing cytology. <i>Mod Pathol</i> . 2006 Jul;19(7):907-13.	EXCLUDED M-C
18. Fasanella KE, McGrath KM, Sanders M, Brody D, Domsic R, Khalid A. Pancreatic endocrine tumor EUS-guided FNA DNA microsatellite loss and mortality. <i>Gastrointestinal</i>	INCLUDED

Endoscopy. 2009 In press. E-published Jan 17, 2009.	
19. Lin X, Finkelstein SD, Zhu B, Ujevich BJ, Silverman JF. Loss of Heterozygosities in Barrett Esophagus, Dysplasia and Adenocarcinoma detected by Esophageal Brushing Cytology and Gastroesophageal biopsy. Cancer Cytopathology. Feb. 2009, 117(1): 57-66.	EXCLUDED M-C
20. Lin X, Finkelstein SD, Zhu B, Silverman JF. Molecular analysis of multifocal papillary thyroid carcinoma. J Mol Endocrinol. 2008. 41(4):195-203.	EXCLUDED M-C
21. Zolotarevsky E, Kwon RS, Piraka CR, Wamsteker EJ, Elta GH, Simeone DH, Scheiman J, Pedroza JM, Anderson MA. Endoscopic Ultrasound with Fine Needle Aspiration (EUS-FNA) with Pancreatic Cyst Fluid DNA Analysis Influences Clinical Management in Patients with Cystic Lesions of the Pancreas. Gastrointestinal Endoscopy. 2007 65(5):AB193. Abstract presented at DDW2007.	EXCLUDED – NOT A FULL PUBLICATION

OTHER PUBLIC REVIEW COMMENTS

(Note that essentially all the public comments pertain to suggestions to include additional papers)

The EPC reviewed the suggestions for inclusion. With the exception of the papers described above as “INCLUDED”, all other suggested publications are not eligible for inclusion.