TABLE 1: Opportunities for molecular pathology to influence clinical management of ACP

<table>
<tr><th>When?</th><th>How?</th><th>Example</th></tr>
<tr><td>Diagnosis</td><td rowspan="5">Assessment of cell-free biomarkers e.g. DNA, RNA; proteins, lipids and metabolites in the blood, CSF, cystic fluid, or urine.

A marker could be from the tumor itself or reflect damage, e.g., to the hypothalamus</td><td rowspan="5">*BRAF* mutation detectable in plasma of patients with PCP (Brastianos et al., 2016)

Identification of matrix metalloproteinases in urine of patient with recurrent ACP (Smith et al., 2007)</td></tr>
<tr><td>Risk stratification for surgery</td></tr>
<tr><td>Risk stratification of risk of relapse</td></tr>
<tr><td>Assessment of response to radiotherapy</td></tr>
<tr><td>Early detection of relapse</td></tr>
<tr><td>Novel solid tumor therapies</td><td>Targeting pathways in the tumor tissue or targeting the host response to the tumor</td><td rowspan="2">The use of BRAF inhibitors in PCP (Alywin et al., 2015; Brastianos et al., 2016)</td></tr>
<tr><td>Novel cystic therapies</td><td>Targeting pathways leading to cyst formation</td></tr>
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Novel therapies for sequelae	Novel treatments for hypothalamic obesity	Attempted use of GLB1 agonists in treatment of hypothalamic obesity (Zoicas et al., 2013)

TABLE 2: Pathways implicated in ACP pathogenesis and their therapeutic opportunities

Pathway	Evidence of Deregulation	Therapeutic Opportunities
WNT pathway (Martinez-Barbera & Buslei, 2015; Larkin & Ansorge, 2013; Kahn, 2014)	The majority of ACPs have somatic activating mutations in exon 3 of *CTNNB1*. These prevent degradation of the protein β-catenin leading to pathway activation. Surprisingly nucleo-cytoplasmic activation is only seen in a small proportion of cells, often correlating with epithelial whorls and referred to as "clusters."	The WNT pathway plays crucial roles in development and tissue homeostasis making it challenging to safely target. Commonly disrupted in many tumor types considerable efforts are underway to target this pathway however no therapies have been approved and few have made it to clinical trial. Any approach for craniopharyngioma must target the pathway downstream of β-catenin.
SHH pathway (Andoniadou et al., 2012; Gump et al., 2015; Gomes et al., 2015; Gould et al., 2014; Sekulic et al., 2012; Lee et al., 2014; Rhim et al., 2014)	SHH has been shown to be over-expressed in ACP in several studies. SHH is expressed by clusters in human and murine ACP with PTCH1	Several SHH pathway inhibitors have been developed, of which the smoothened inhibitor vismodegib is licensed for use in basal cell carcinoma. Despite initial optimism SHH pathway inhibitors have been disappointing in tumors with paracrine signaling

	expressed in palisading epithelium suggesting paracrine signaling.	as opposed to mutational activation. In some cases inhibition has resulted in tumor promotion.
EGFR pathway (Holsken et al., 2011; Stache et al., 2014)	EGFR phosphorylated in human ACP clusters and cells neighboring invasion. EGFR phosphorylated in primary ACP cultures. Inhibition reduces migration. EGFR phosphorylated in clusters in xenograft model at leading edge of tumor invasion.	Several generations of EGFR inhibitors have been developed and are in routine use in some tumor types, e.g., non-small cell lung cancer.
Inflammation (Pettorini et al., 2010; Martelli et al., 2014; Gong et al., 2014; Zitvogel et al., 2015)	Inflammatory infiltrates (e.g., lymphocytes) are observed in tumor specimens. High levels of IL6, ILA, TNF, and α-defensins 1-3 have been identified in	A possible mechanism of action of IFNα is through modulation of the immune response. A range of agents are available for broad (e.g. steroids, NSAIDS) or more targeted immune suppression (e.g., anti-TNF, anti-IL6R agents) are

	cystic fluid, and leakage can lead to inflammation. High levels of CXCR4 and CXCL12 associated with increased recurrence. Clusters in murine ACP express high levels of inflammatory mediators.	available and widely used in other conditions but with minimal effect on tumors.