by tumour origin, performance status, and previous somatostatin analogue treatment. The primary endpoint was progression-free survival assessed by central radiology review, and overall survival was a key secondary endpoint. Median progression-free survival was 11·0 months (95% CI 9·2–13·3) in the everolimus group and 3·9 months (3·6–7·4) in the placebo group, hazard ratio (HR) 0·48 (95% CI 0·35–0·67). A non-significant benefit in improved survival was also observed in an interim overall survival analysis (HR 0·64 [95% CI 0·40–1·05]). A retrospective analysis showed consistent beneficial effects across subgroups based on the primary tumour origin (ie, lung, gastrointestinal, or neuroendocrine neoplasms of unknown primary). A positive treatment effect regardless of the extent of liver metastases was also noted.[12] Everolimus therefore shows significant antitumour efficacy in lung neuroendocrine neoplasms as well as gastrointestinal, including duodenal, small intestinal, and rectal, tumours.

Everolimus, by targeting the mTOR pathway, has shown significant antitumour efficacy in most well-differentiated neuroendocrine neoplasms (NET G1 and G2) and provides a valid alternative for treatment of malignant neuroendocrine neoplasms. However, competitors exist for treatment of small intestinal tumours in the form of somatostatin analogues and peptide receptor radiotherapy. For pancreatic neuroendocrine neoplasms, tyrosine-kinase inhibitors (sunitinib) and cytotoxic treatments (temozolomide and capecitabine) are treatment options. Everolimus has significantly contributed to the understanding of treatment options for neuroendocrine neoplasms, but the drug's precise place in the treatment algorithm needs to be further analysed in studies comparing other treatment alternatives.

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1 Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol* 2008; **26:** 3063–72.
2 Bosman FT, Carneiro F. WHO classification of tumours, pathology and genetics of tumours of the digestive system. Lyon: IARC Press, 2010.
3 Rindi G, Kloppel G, Couvelard A, et al. TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system. *Virchows Arch* 2007; **451:** 757–62.
4 Rinke A, Muller HH, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol* 2009; **27:** 4656–63.
5 Caplin ME, Pavel M, Cwikla JB, et al, for the CLARINET Investigators. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med* 2014; **371:** 224–33.
6 Strosberg JR, Fine RL, Choi J, et al. First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas. *Cancer* 2011; **117:** 268–75.
7 Pavel M, Baudin E, Couvelard A, et al. ENETS consensus guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary. *Neuroendocrinology* 2012; **95:** 157–76.
8 Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med* 2011; **364:** 501–13.
9 Meric-Bernstam F, Gonzalez-Angulo AM. Targeting the mTOR signaling network for cancer therapy. *J Clin Oncol* 2009; **27:** 2278–87.
10 Yao JC, Lombard-Bohas C, Baudin E, et al. Daily oral everolimus activity in patients with metastatic pancreatic neuroendocrine tumors after failure of cytotoxic chemotherapy: a phase II trial. *J Clin Oncol* 2010; **28:** 69–76.
11 Pavel ME, Hainsworth JD, Baudin E, et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. *Lancet* 2011; **378:** 2005–12.
12 Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med* 2011; **364:** 514–23.
13 Yao JC, Fazio N, Singh S, et al, for the RAD001 in Advanced Neuroendocrine Tumours, Fourth Trial (RADIANT-4) Study Group. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet* 2015; published online Dec 15. http://dx.doi.org/10.1016/S0140-6736(15)00817-X.

Fetal alcohol spectrum disorder: complexity from comorbidity

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Every day, in the USA alone, 100–500 children are estimated to be born with fetal alcohol spectrum disorders (FASD).[1] Most will never be diagnosed with FASD, and those who are will often wait years for a correct diagnosis. Misdiagnosis is often due to an underappreciation of the role of damage to the CNS, which is a unifying concept in FASD. The expression of the FASD phenotype is both age and development dependent. Increasing prevalence of comorbidity is key to understanding the typical increase in FASD severity over time.[2]

In *The Lancet*, Svetlana Popova and colleagues[3] present data expanding the phenotype for FASD. Using an extensive review of published literature, they examine the prevalence of comorbidity in FASD and show that FASD is a multisystem disorder. They note that disorders affecting the CNS and sensory impairments are very common, affecting 50–91% of people with FASD. Clinical experience shows that disorders of brain function are often the primary drivers of the lifelong impairments typical of FASD.

The public health dimensions of FASD can be readily appreciated: FASD is a highly prevalent disorder (at least as common as autism spectrum disorders), is the leading identifiable cause of intellectual disability, and results in very high costs to society (annual cost of care exceeds US$3·6 billion in the USA).[4] Most people with FASD require care over much of their lifetime. FASD is highly recurrent within sibships and across generations. People with FASD often seek services from programmes for developmental disabilities, mental health, educational disabilities, foster care, juvenile corrections, and substance abuse treatment. This disorder is also a worldwide issue, with rates of prenatal alcohol exposure and FASD increasing in many low-income and middle-income countries.[5] As a result, both prenatal alcohol exposure and FASD represent large, but potentially preventable, causes of mortality and disability.

What can we do? Some low-cost strategies seem relatively easy to implement. We need to implement FASD screening for children of women in treatment for substance misuse or who are incarcerated, and for all children entering foster care. Early identification enhances opportunities for entry into intervention programmes.

The scarcity of diagnostic services is the most common issue I hear about from parents, professionals, and foster parents. Few, if any, countries have the capacity to use multidisciplinary diagnostic clinics to manage the new cases of FASD born each year. The development of enough multidisciplinary teams with the capacity to assess hundreds of thousands of affected but undiagnosed people is unlikely. However, a welcome and much needed option has recently emerged. The proposed criteria for neurodevelopmental disorders associated with prenatal alcohol exposure (ND-PAE) in the recent revision of the Diagnostic and Statistical Manual of Mental Disorders[6] are timely and clinically useful. The proposed criteria capture a substantial proportion of the most common features of the FASD phenotype. These criteria have the potential to allow diagnosis for large numbers of people with FASD by paediatricians, psychiatrists, neurologists, and other providers of mental health and developmental disability services. Diagnostic clinics should offer long-term follow-up, since FASD changes over time, and a diagnosis of FASD at 4 years of age might be of limited help in determining the needs of adolescents or adults.

Our understanding of the full range of the FASD phenotype is currently limited by a scarcity of studies in both adult and geriatric populations. Mortality is also an underappreciated part of the FASD phenotype.[7] FASD increases mortality risk in affected children and their siblings (whether or not they have a diagnosis of FASD), and it is a marker for a great increase in risk of death for the mother.[8] As yet we have very little information about a possible mortality risk associated with FASD for fathers. As the data from Popova and colleagues[3] indicate, nearly all specialties in medicine and allied health are likely to encounter and treat people with FASD.


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Prevention efforts should focus on identification of alcohol use before and during pregnancy. Identification of FASD in young children has the additional benefit of identifying a woman who is at more than 70% risk to have another affected child if she continues to drink during subsequent pregnancies. Anticipatory guidance should also emphasise prevention and early recognition of what are termed secondary disabilities in FASD (ie, school failure, substance abuse, multiple foster home placements, peer exploitation, incarceration, and premature death). These are potentially preventable issues. An effective response will require that we all join this effort with awareness that FASD is mostly undiagnosed and, as a result, is inappropriately treated in most health-care settings. Let's start with an emphasis on primary prevention in settings providing health care for women by asking the question "when was your last drink?".

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1 May PA, Baete A, Russo J, et al. Prevalence and characteristics of fetal alcohol spectrum disorders. *Pediatrics* 2014; **134:** 855–66.
2 Burd L, Klug MG, Martsolf JT, et al. Fetal alcohol syndrome: neuropsychiatric phenomics. *Neurotoxicol Teratol* 2003; **25:** 697–705.
3 Popova S, Lange S, Shield K, et al. Comorbidity of fetal alcohol spectrum disorder: a systematic review and meta-analysis. *Lancet* 2015; published online Jan 5. http://dx.doi.org/10.1016/S0140-6736(15)01345-8.
4 Lupton C, Burd L, Harwood R. Cost of fetal alcohol spectrum disorders. *Am J Med Genet C Semin Med Genet* 2004; **127C:** 42–50.
5 Williams AD, Nkombo Y, Nkodia G, et al. Prenatal alcohol exposure in the Republic of the Congo: prevalence and screening strategies. *Birth Defects Res A Clin Mol Teratol* 2013; **97:** 489–96.
6 American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, fifth edition. Arlington, Virginia: American Psychiatric Publishing, 2013.
7 Burd L, Klug MG, Bueling R, et al. Mortality rates in subjects with fetal alcohol spectrum disorders and their siblings. *Birth Defects Res A Clin Mol Teratol* 2008; **82:** 217–23.
8 Li Q, Fisher WW, Peng CZ, et al. Fetal alcohol spectrum disorders: a population based study of premature mortality rates in the mothers. *Matern Child Health J* 2012; **16:** 1332–37.