Clone detection with multicolour FISH

<table>
<thead>
<tr>
<th>“Genotype”</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>2222</td>
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</tr>
<tr>
<td>3212</td>
<td>20</td>
</tr>
<tr>
<td>2112</td>
<td>8</td>
</tr>
<tr>
<td>2221</td>
<td>2</td>
</tr>
</tbody>
</table>

Shannon diversity = 1.23
Richness = 4

Martinez et al., Nat Comms 2016
Diversity remains stable

- No linear relationship between time (between brushes) and difference in diversity
  - Clones appear and disappear dynamically: evolutionary stasis.

Martinez et al., Nat Comms 2016
Glands with a ‘recent ancestry’ are typically confined to small groups. Neighbouring glands show recent ancestry, while distant glands do not. Only small clonal expansions are seen. 

Shahab Khan, unpublished
Gland phenotype diversity increases with progression.
Are goblet cell glands really a biomarker of increased cancer risk?

Â A differentiated cell that is lost through cell turnover
Â Several studies have shown goblet cell Barrett’s to have a higher risk than non-goblet cell glands

Â This is because they compare cases with diverse phenotypes with homogenous cases!
Barrett glands are clones and are capable of division through fission

Glands contain a hierarchy of differentiated epithelial cells and glands can evolve from one phenotype to another

Barrett’s glands strongly resemble pyloric gastric glands with intestinal metaplasia – does Barrett’s originate from the stomach?

First demonstration of a clonal link between non-goblet metaplastic glands (CLO) and invasive cancer

Barrett’s dysplasia retains the stem cell architecture of non-dysplastic glands and shows 3 major phenotypes, with foveolar type most common

Diversity, both genetic and phenotypic, is strongly associated with, and can predict oesophageal cancer

The clonal dynamics of Barrett’s is now becoming better understood, where those patients not at risk show evolutionary stasis with little evidence of clonal sweeps. Those at risk may (or may not) show a change in these dynamics but there is significantly more diversity
Models of the genetic evolution of Barrett’s to cancer
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Using either the median or the upper quartile to define high risk:
- High stratifying potential

Martinez et al., Nat Comms 2016
Dysplastic Barrett’s is polyclonal

Multiple different clones can give rise to dysplasia

Ross-Innes et al., Nat Genetics 2015