

# RECRUITING AND PHENOTYPING IN FAMILY STUDIES

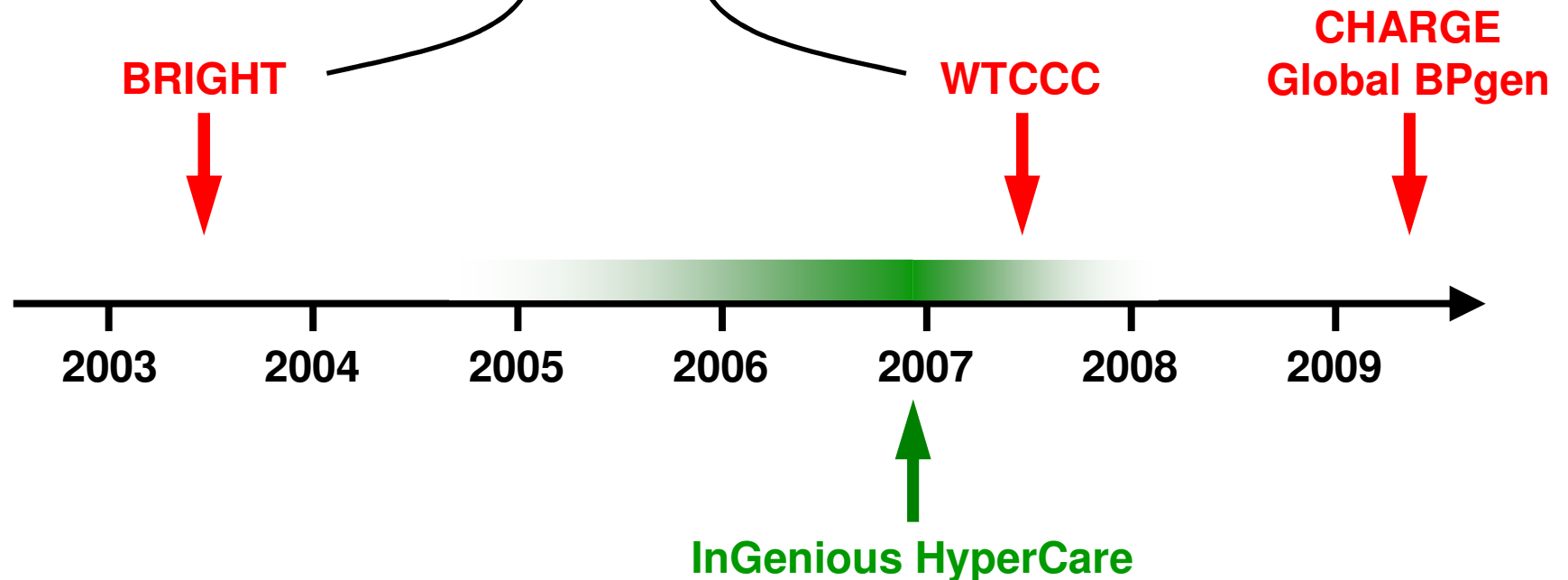
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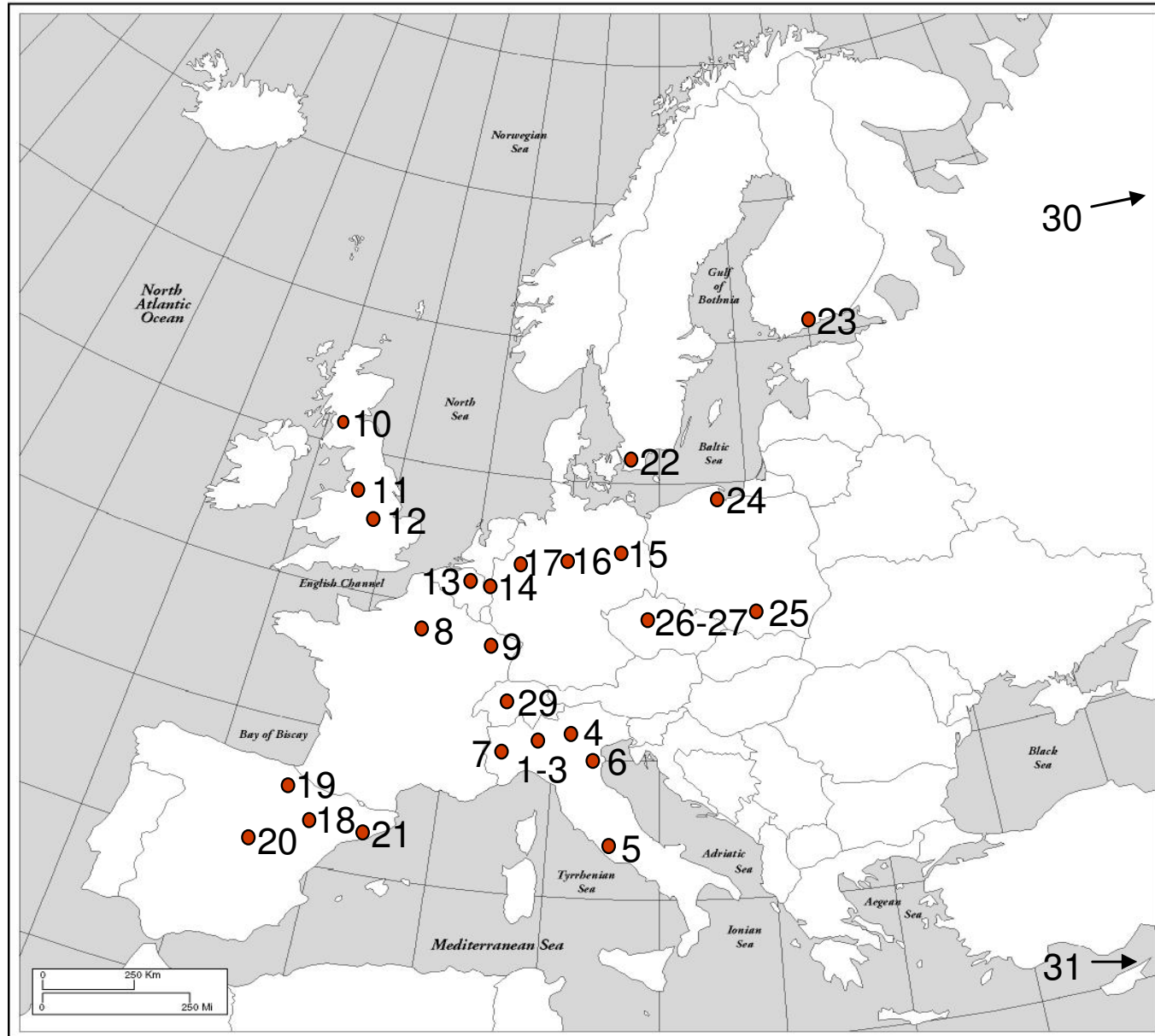


GWAS using microsatellite markers  
2010 affected sibling pairs  
Severe hypertension  
Extensive phenotyping

GWAS using Affymetrix 500k  
2000 patients and 3000 controls  
Severe hypertension  
No phenotyping of controls



- **Related subjects are more likely to share disease-causing genetic variants**
- **Better suited to detect rare variants in case of locus and allele heterogeneity**
- **Controlling for the effects of shared environment**
- **Robust to population stratification**



- **European multicentre study**
- **Families ascertained and enriched for severe hypertension**
- **Extensive phenotyping**
  - **Blood pressure and target organ damage**
  - **Microinflammation**
  - **Microalbuminuria**
- **Follow-up**

**Patients of either sex who**

- are not older than 60 years at the time of enrolment.
- were diagnosed to have essential hypertension before the age of 50 years

**At the time of recruitment:**

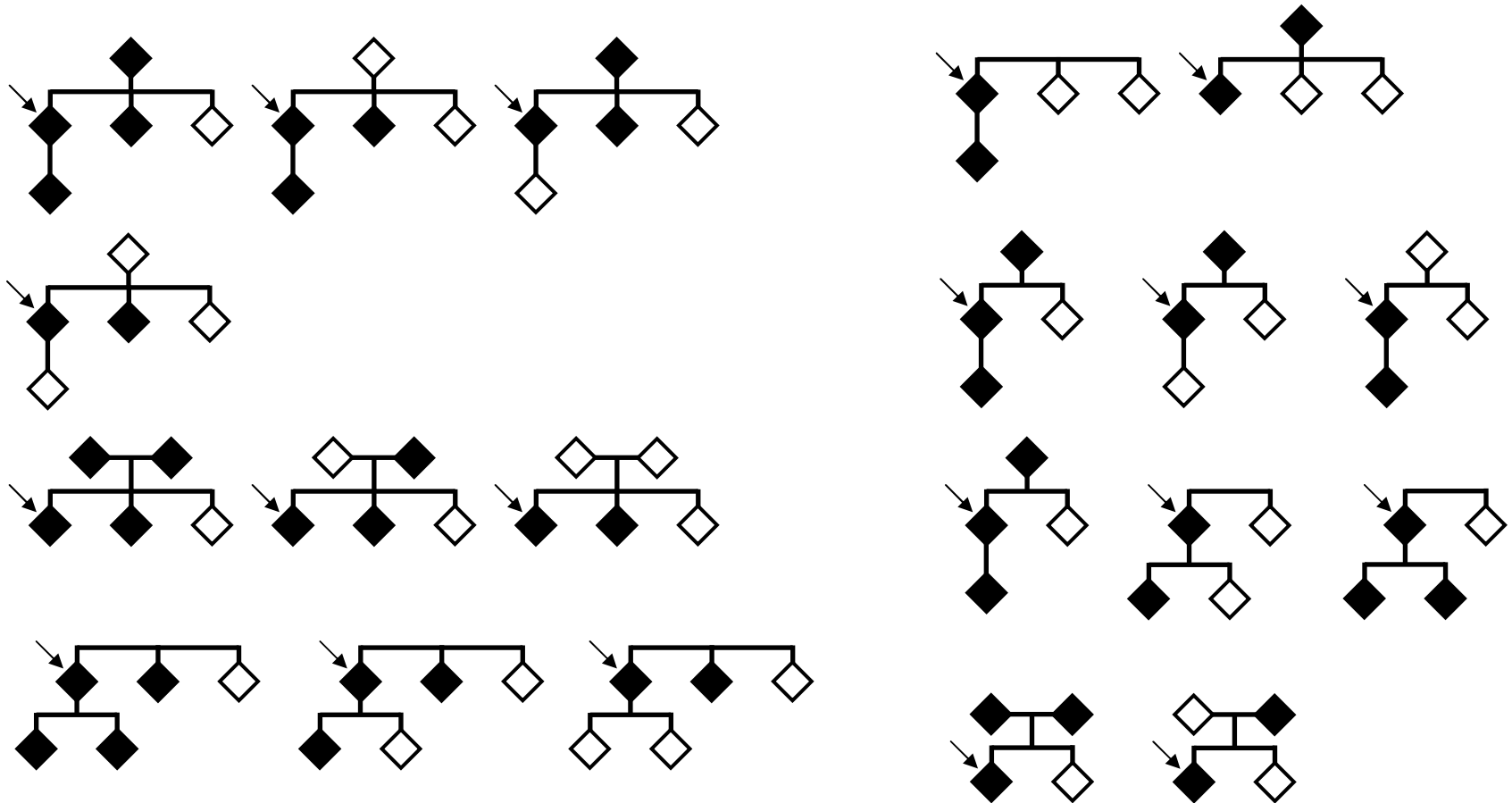
- If untreated, have SBP >160 mmHg or DBP >95 mmHg
- If treated are on  $\geq 2$  different antihypertensive drugs

**Family criteria:**

- $\geq 3$  first-degree relatives
- $\geq 1$  family member with hypertension
- from  $\geq 2$  generations

- Any known form of **secondary hypertension**, including sleep apnoea syndrome
- Any known **previous clinical complications of hypertension** (angina, MI, stroke, TIA, peripheral artery disease) at any time
- Any known **renal disease**, including GFR < 60 mL/min/1.73 m<sup>2</sup> as estimated by the abbreviated MDRD formula, or kidney stones
- Kidney or other organ transplantation
- Type 1 diabetes mellitus
- **Heart failure stage D** (AHA/ACC criteria)
- Any **malignant concomitant diseases** or history of malignant diseases within the last five years, with exception of treated squamous skin cancer or basalioma
- Clinical or laboratory signs of acute infection, especially urinary tract infection
- Systemic inflammatory diseases, such as autoimmune diseases, connective tissue diseases or collagenoses.
- Steroids or any other immunosuppressive drug
- Severe known liver disease (ALT or  $\gamma$ -GT above three-fold of upper normal limit)
- Current **alcohol** intake of more than 21 drinks/week.

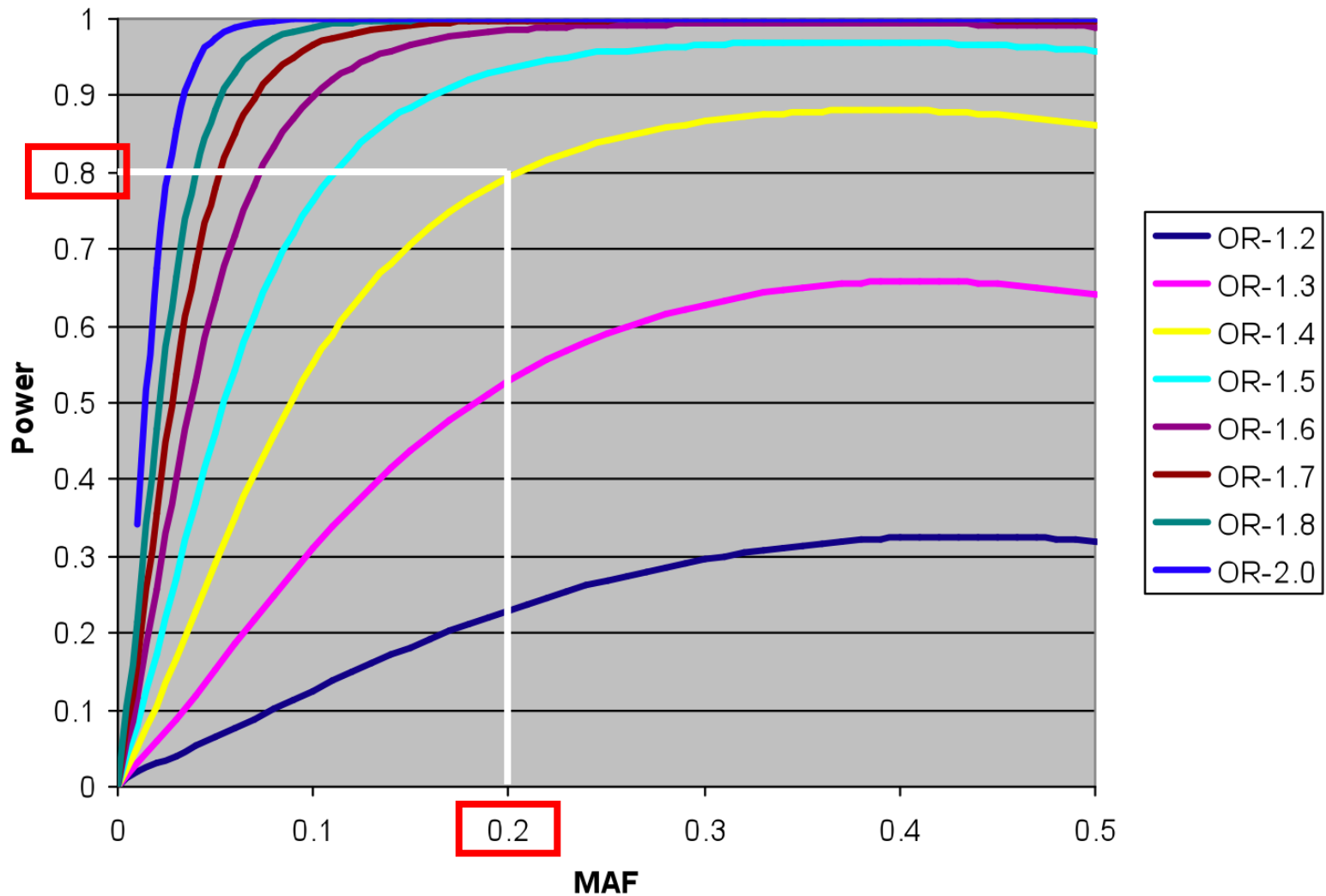
# Examples of Possible Family Structures



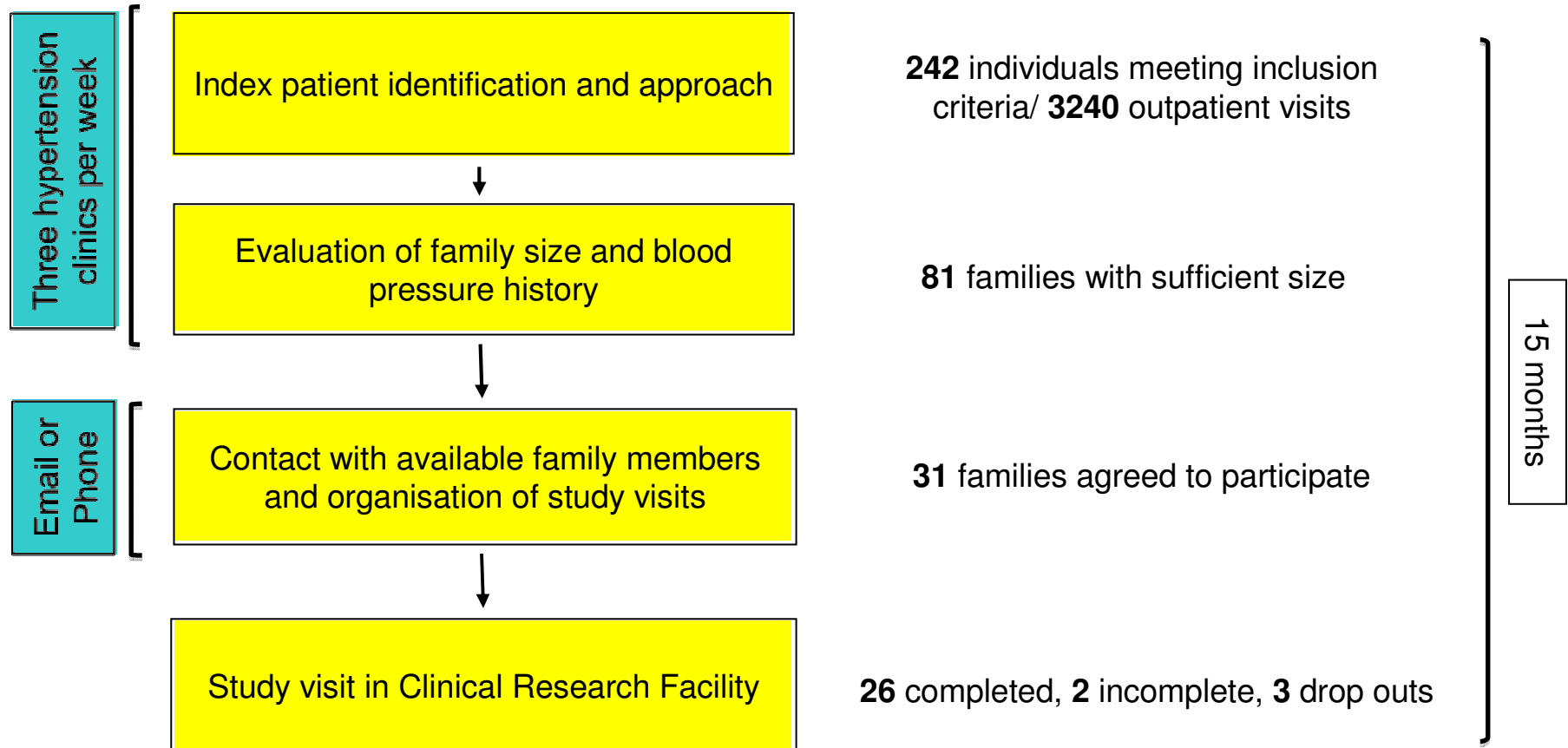
- At least 4 family members
- At least 2 subjects with hypertension
- At least 2 generations

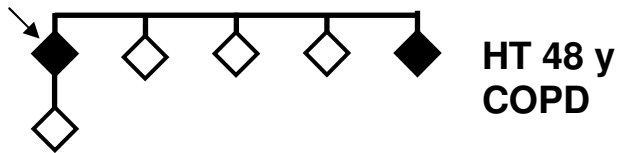
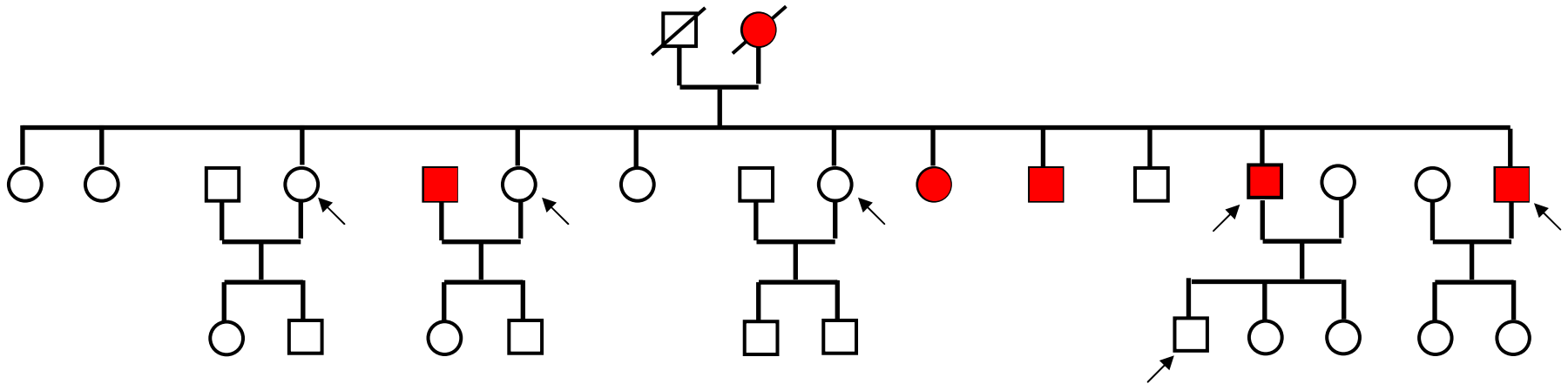
◆ affected  
 ◇ unaffected  
 ↘ index patient

1000 families - 3 offspring, 1 parent - 2 affected - disease prevalence 20%

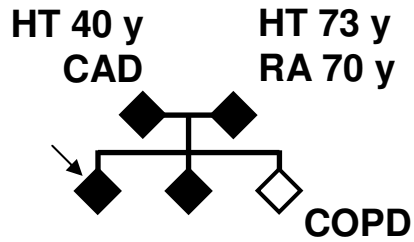
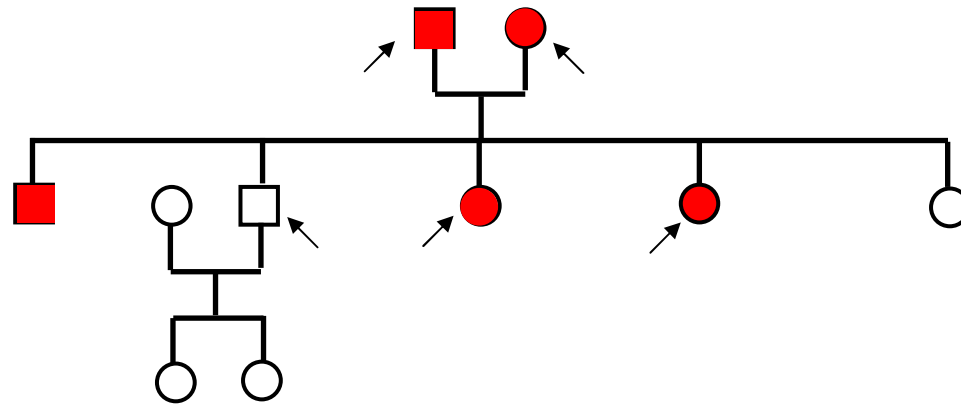


# Recruitment Strategy in Glasgow

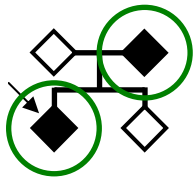
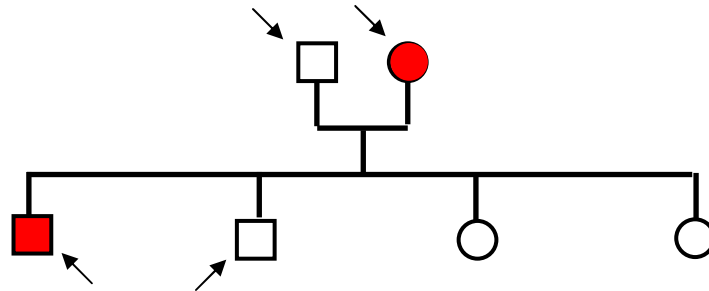




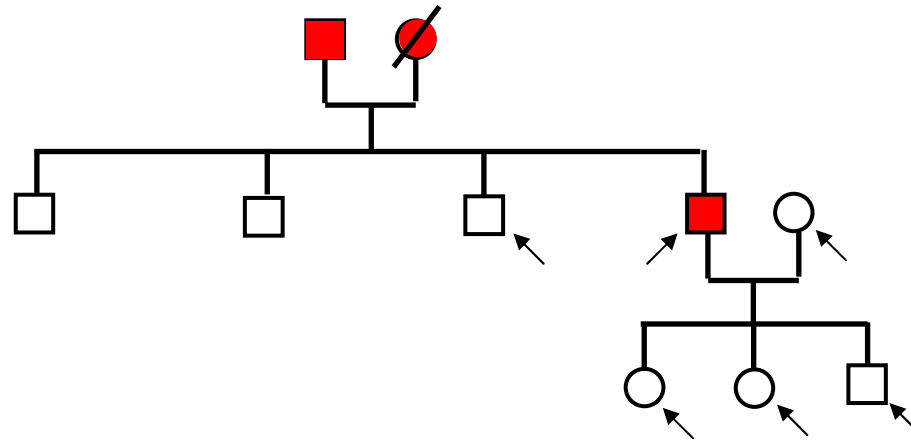
**Hypertension at 47 years**



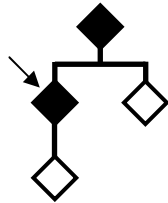
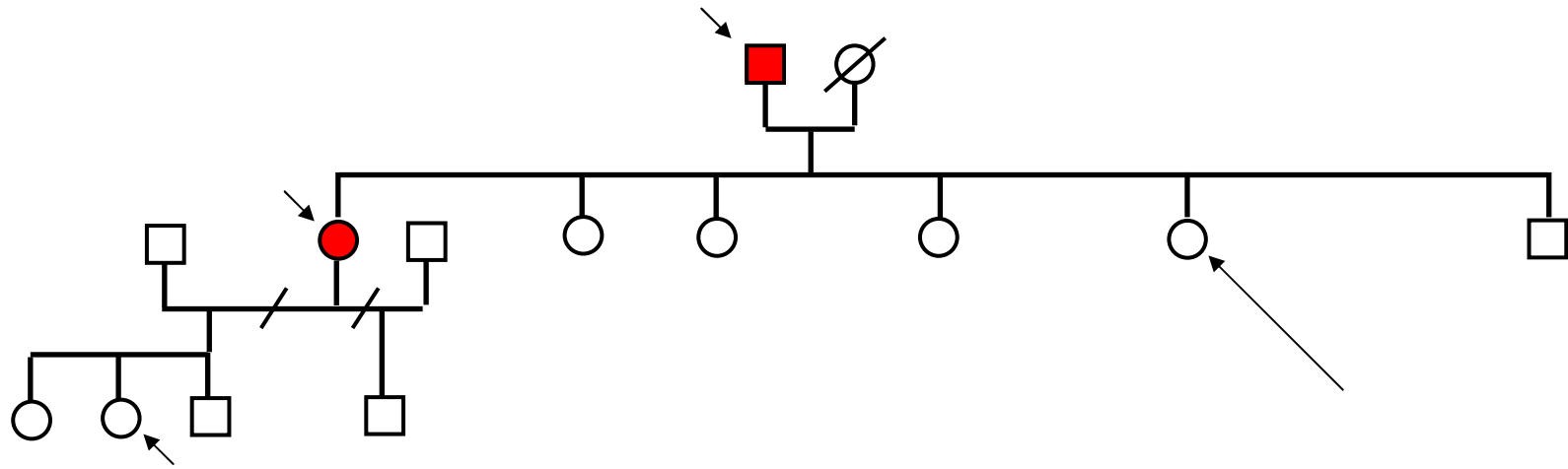
**Hypertension at 39 years**



**Hypertension aged 30 years**



**Hypertension aged <50 years**

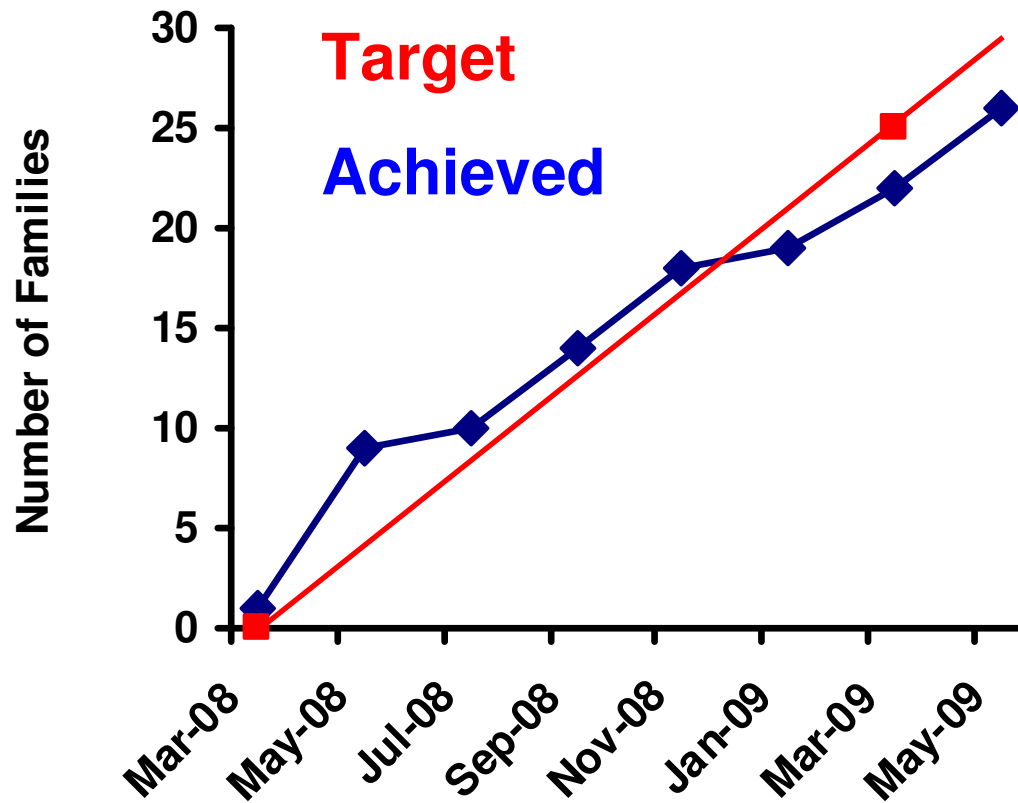


**Hypertension at 49 years**

	<b>Index Patients</b>	<b>Hypertensive Family Members</b>	<b>Normotensive Family Members</b>
<b>Sex [m/f]</b>	<b>13 / 15</b>	<b>20 / 29</b>	<b>18 / 33</b>
<b>SBP [mmHg]</b>	<b>152 ± 22</b>	<b>150 ± 20</b>	<b>127 ± 13</b>
<b>DBP [mmHg]</b>	<b>94 ± 11</b>	<b>87 ± 12</b>	<b>75 ± 11</b>
<b>BMI [kg/m<sup>2</sup>]</b>	<b>30.5 ± 4.0</b>	<b>29.2 ± 6.0</b>	<b>25.0 ± 4.8</b>
<b>Age [y]</b>	<b>47 ± 8</b>	<b>55 ± 15</b>	<b>31 ± 11</b>
<b>Age at onset [y]</b>	<b>40 ± 9</b>	<b>46 ± 13</b>	<b>-</b>
<b>Treated [yes/no]</b>	<b>24 / 4</b>	<b>34 / 15</b>	<b>-</b>

	<b>Index Patients</b>	<b>Hypertensive Family Members</b>	<b>Normotensive Family Members</b>
<b>ACR [mg/mmol]</b>	<b>2.6 ± 5.8</b>	<b>1.9 ± 2.5</b>	<b>1.7 ± 2.6</b>
<b>Creatinine [μmol/L]</b>	<b>79 ± 14</b>	<b>77 ± 17</b>	<b>74 ± 14</b>
<b>CRP [mg/L]</b>	<b>3.1 ± 2.0</b>	<b>4.1 ± 4.6</b>	<b>3.9 ± 5.4</b>
<b>WBC [nL<sup>-1</sup>]</b>	<b>7.2 ± 1.9</b>	<b>7.7 ± 2.4</b>	<b>7.1 ± 2.1</b>
<b>LV mass [g/m<sup>2.7</sup>]</b>	<b>46 ± 12</b>	<b>47 ± 18</b>	<b>38 ± 10</b>
<b>Central PP [mmHg]</b>	<b>48 ± 18</b>	<b>51 ± 18</b>	<b>37 ± 12</b>
<b>Pulse Wave Velocity [m/s]</b>	<b>8.1 ± 1.2</b>	<b>9.4 ± 2.5</b>	<b>6.6 ± 1.4</b>

<b>Participants</b>	<b>127</b>
<b>Echocardiography</b>	<b>126</b>
<b>Carotid ultrasound</b>	<b>126</b>
<b>ECG</b>	<b>121</b>
<b>PWA</b>	<b>89</b>
<b>PWV</b>	<b>63</b>
<b>ABPM</b>	<b>56</b>



**Aim:**  
50 families / 2 years

**May 2009:**  
- 26 families completed  
- 2 families in progress



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