

Bone Marrow Registries and Donor Motives

Ted Bergstrom,
Rod Garratt,
Damien Sheehan-Connor
UCSB

Background

- Bone marrow transplants dramatically improve survival prospects of leukemia patients.
- For transplants to work, donor must be a genetic match for recipient.
- Only 30% of patients have matching sibling.
- U.S. bone marrow registry started in 1986
- Similar registries in other countries (Canada, 1989).

Background

- Bone Marrow Registry contains 6 million people in US and roughly 12 million worldwide
- These people have promised to undergo a painful, somewhat risky procedure to help save a strangers life if asked
- Why do people join the registry?
 - There is an episode of the HBO show "Curb Your Enthusiasm" in which the comedian Richard Lewis needs a kidney transplant and Larry David (the creator of Seinfeld) vows to donate his, thinking he won't be a match. Larry is horrified to learn he actually is a match, and goes to ridiculous lengths to get out of it by trying to find Richard a "better" match. Larry was clearly a pledge donor.
- Is the registry the “right” size? the “right” composition?

Some Genetics

- Individuals “type” is controlled by 6 alleles, located in three loci, called HLA-A, HLA-B and HLA-DR.
 - HLA = Human Leukocyte Antigen
- You inherit a string of 3 from Mom and another string of 3 from Pop.
- Diploid reproduction, each parent has two strings, randomly picks one to give to you.
- String inherited from a single parent called a haplotype.

Possible combinations

- There are about 30 possible alleles that could go in each of the first two loci, and about 10 possibilities for the third.
- All that matters is what 6 alleles you have (phenotype), not who you got them from.
- Matching phenotypes easier than matching genotypes

Your most likely match

- Probability that two full siblings match is about 1/4. They must receive same string from Mom and also same string from Pop. Chance of this is $1/2 \times 1/2 = 1/4$.
- Note that chance of a match with a parent is very small. Same for uncles and aunts and cousins, etc.

Matching a Stranger

- Not all gene combinations on chromosome are equally likely
- Makes estimating match probabilities difficult
- Biologists used phenotype data from the bone marrow registry (included sample of about 400,000 “fully” typed people).
- Biologists observed phenotypes, but not full genotypes. That is, they see what 6 genes each person has, but don't know how they were linked on parental chromosomes.

Clever statistics

- The sample is not big enough to give good estimates of frequency of rare phenotypes.
- They do a clever trick. They use phenotype distribution and maximum likelihood techniques to estimate distribution of haplotypes.
- With estimated haplotype distribution and assumption of random mating w.r.t HLA type, we can estimate distribution of phenotypes.

How many types?

- About 9 million different relevant types
- Probability that two random people match
 - Both US Caucasian : $1/11,000$
 - Both Afr-American: $1/98,000$
 - Both Asian-American: $1/29,000$
 - Afr Am and Caucasian : $1/113,000$
- In contrast to blood transfusions.

Distribution of type size is very nonuniform

- About half the Caucasian population are in groups smaller than $1/100,000$ of population.
- About 20 per cent are in groups smaller than $1/1,000,000$ of population.

Social benefits from an additional donor: Behind the Veil of Ignorance

- Every person in society faces some small probability of needing a life-saving transplant.
- Adding a donor increases the probability of a match for any person.
- We numerically calculate effect of an extra registrant on lives saved and value this increment at the “value of a statistical life” .
- VSL estimated to be about \$6.5 million (Viscusi-Aldy)

Probability of having no match

- Let p_i^x be fraction of the population of race x that is of HLA type i .
- Probability that a person of type i has no match in the registry is

$$\prod_x (1 - p_i^x)^{R_x}$$

- Probability that a randomly selected person of race x has no match in the registry is

$$\sum_i p_i^x \prod_x (1 - p_i^x)^{R_x}$$

Some Differences by Race

Race	Number in Registry	Fraction Available	Effective No. in Registry	Prob. of no Match
Caucasian	4,444,335	.65	2,888,818	.08
Afr-Am	485,791	.34	165,169	.38
Asian-Am	432,293	.44	190,209	.21
Hispanic	594,801	.47	279,556	.16
Nat. Am.	70,781	.48.	33,975	.11

Gain from extra registrant of race x

- Calculate the derivative with respect to R_x of the probability of no match.
 - Derivative applies to each search.
- Multiply this by the number of people seeking matches to find the expected annual number of additional matches resulting from one more registrant.
- Multiply number of additional matches by .21 to get expected number of lives saved.

Expected Annual Lives Saved by 1,000 More Registrants

Race of New Registrant

	Caucasian	Afr-Am	Asian-Am	Hisp	Nat Am
Lives Saved	0.009	0.035	0.015	0.016	0.01

Two things going on here:

1. Gain in match probability for black from adding additional black registrant is over 20 times gain for Caucasian of adding an additional Caucasian because additional black is far less likely to be redundant.
2. However, many more Caucasian searches (2,500) than black searches (200).

Annual flow

- A registrant can remain in registry until age 61.
- Median age of registrants is 35.
- We assume that registrants remain in registry for 25 years, on average.
- We discount benefits appearing in later years.

Present Value of Lives Saved by Additional Registrant

Race of Additional Registrant

Present value to this group	Caucasian	Afr- Am	Asian -Am	Hispanic	Nat Am
Caucasian	\$1,012	\$961	\$664	\$1,028	\$928
Afr-Am	\$71	\$3,155	\$81	\$285	\$150
Asian-Am	\$27	\$44	\$1,063	\$60	\$59
Hispanic	\$91	\$341	\$132	\$701	\$190
Nat Am	\$5	\$10	\$8	\$11	\$37
Total Value	\$1,206	\$4,512	\$1,947	\$2,085	\$1,364

Costs

- Cost of tests and maintaining records about \$105 per registrant.
- Physician and hospital costs of transplants is around \$166,000.

Effective Registry

- Need to register more than one person to make one effective registrant
- Varies by race (Kollman et al.)
 - 1.6 Caucasians
 - 2.9 Afr. Am.
- Inflates costs differently across races
- Also number of transplants resulting from registrant differs across race

Benefit Cost Comparison: Present values of new registrant

	Caucasian	Afr- Am	Asian- Am	Hispanic	Nat Am
Benefit	\$1,206	\$4,512	\$1,947	\$2,078	\$1,364
Cost	\$297	\$800	\$446	\$455	\$359
B/C Ratio	4.1	5.6	4.4	4.6	3.8

Costs include typing and storage, but also these numbers are multiplied by factors needed to reflect an effective registrant. That is why they are so different.

Optimal Registry Sizes

- Larger registry is called for on efficiency grounds
- As registry gets larger new registrants add less
- Calculating optimal registry is complicated by cross matches
- In optimal registry the marginal benefit to persons of all races from adding an additional registrant of any race is equal to the marginal cost.

Actual and Optimal Registry; Number in Millions

Race	Actual Number	Optimal Number	Ratio	% of Eligible Pop.
Caucasian	4.44	12.11	2.72	7.1
Afr-Am	0.49	4.73	9.75	23.8
Asian-Am	0.43	1.76	4.07	26.5
Hispanic	0.59	2.93	4.93	14.3

Current and Steady-State Optimal Registrants per Year

Race	Current annual new registrants	Annual registrants for optimal steady state	Ratio optimal to current	% of Eligible Pop.
Caucasian	340,000	480,000	1.4	10.5
Afr-Am	30,000	189,000	6.3	17.4
Asian-Am	40,000	70,000	1.8	24.5
Hispanic	45,000	117,000	2.6	12.2

No Match Probabilities

Race	Prob of no match Actual Registry	Prob of no match Optimal Registry
Caucasian	.08	.03
Afr-Am	.38	.12
Asian-Am	.21	.09
Hispanic	.11	.06

What's going on?

- Not a Rawlsian minmax outcome.
 - Philosopher John Rawls reasoned in his book, A Theory of Justice that if one is put behind a "veil of ignorance" about one's future station in life, one will formulate a concept of a just society based on the maximin principle where one maximizes the worst, most oppressive condition one could possibly have in society once the veil is removed.
 - New registrant of each race is most likely to match member of own race. More Caucasian searches means new Caucasian registrants are more valuable.

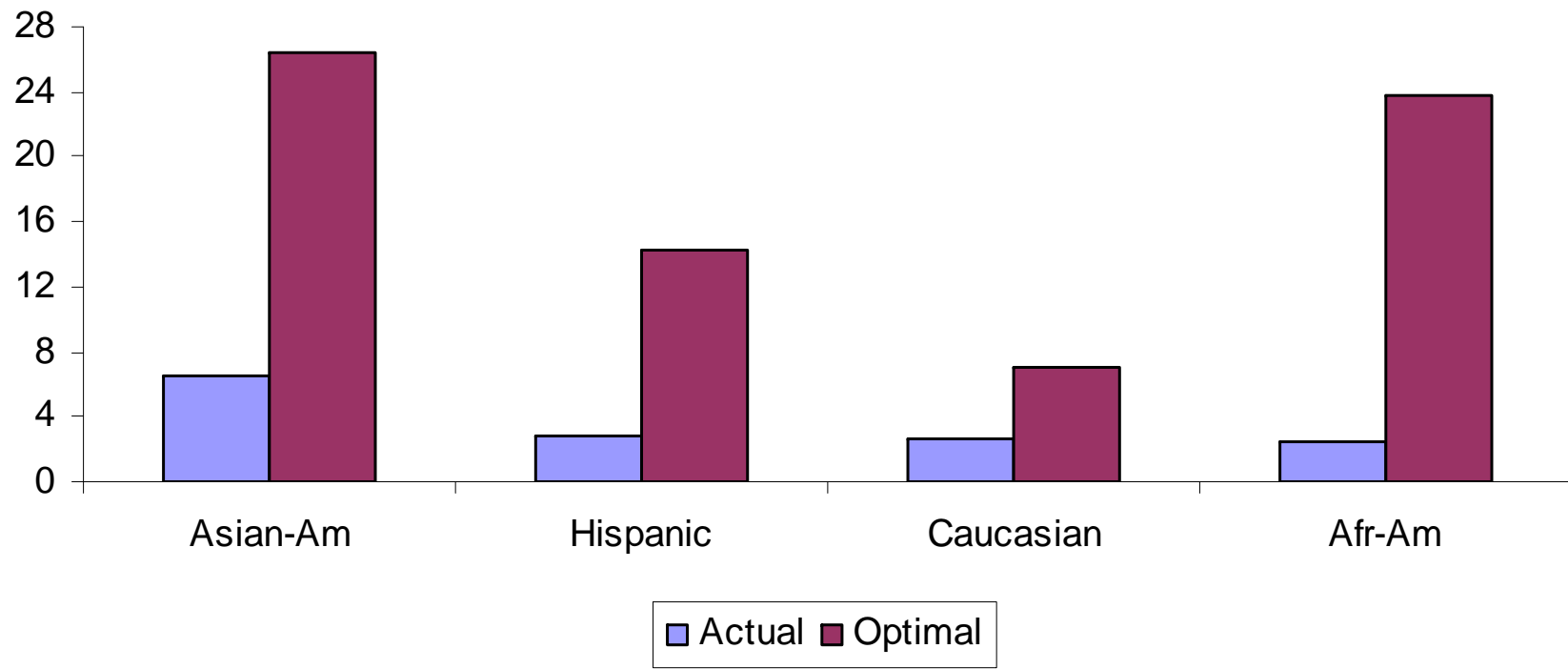
What's going on?

- Social optimum reflects difference in number of people seeking transplants (Increasing returns to scale).
- Difference in costs due to differences in effectiveness rates.

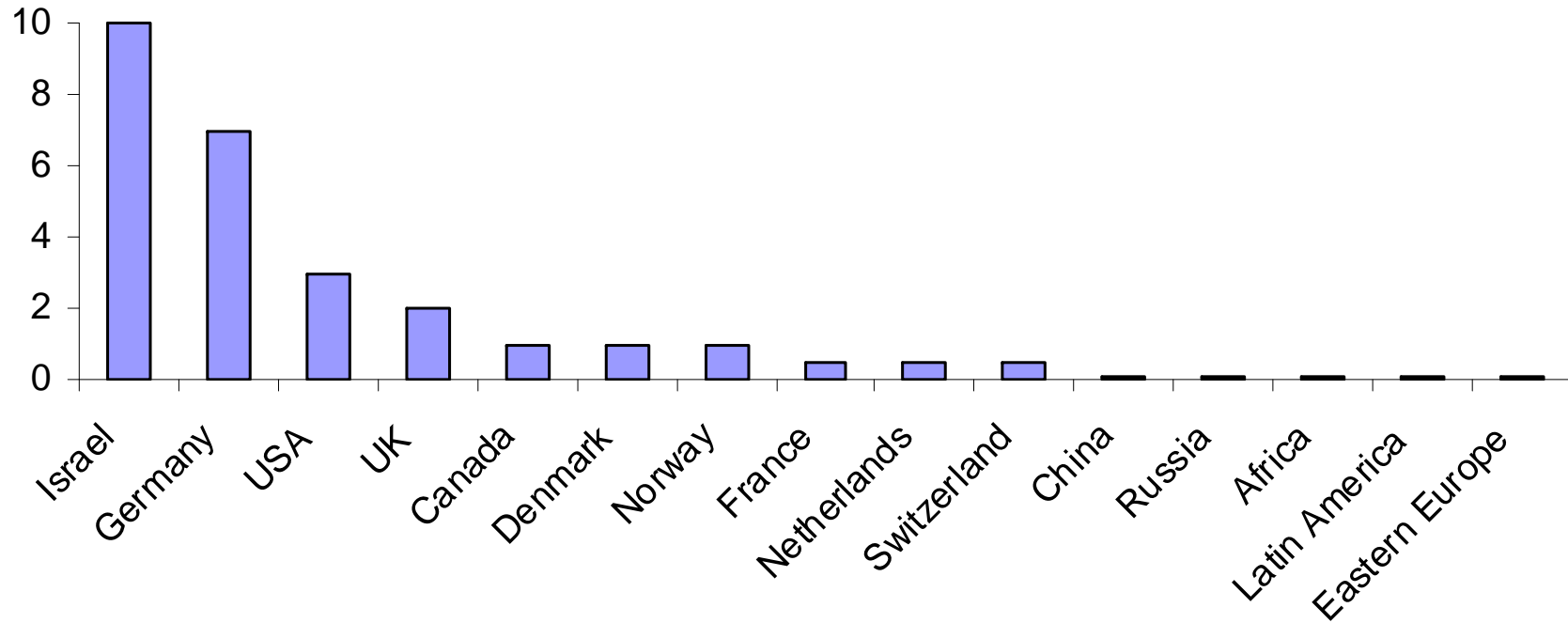
So far...

- Benefit of additional registrant by race
- Size and composition of registry we would like to have if those registrants were available
- Next steps...
 - What motivates individuals to join the registry?
 - Consider world registry

Percent of Population in Registry by Race



Percent of Population in National Registry



Social Optimum

- An optimal size of registry for each country is found by maximizing the difference between the total value of statistical lives saved and the total cost of recruiting and maintaining the registry.

Net benefits to world registry

- $P_j(R)$ is the probability that a randomly selected person in country j has a match in some country when the vector of national registry sizes is R .
- v_j value of statistical life in country j
- s_j probability a resident of country j will need a transplant
- l survival probability, n_j pop. of country j
- Then net benefits from the registry are

$$NB(R) = \sum_j l v_j s_j P_j(R) n_j - \sum_j C_j(R_j)$$

Optimizing conditions

$$\sum_k l v_k s_k \frac{\partial P_k(R)}{\partial R_j} n_k = C'_j(R_j), \quad \forall j$$

- The function $\text{NB}(\mathbf{R})$ is a concave function of the vector \mathbf{R} .
- Therefore a computational hill-climbing algorithm will converge uniquely to an optimum.

Optimal registry is larger than non-cooperative NE

$$-lv_1s_1Q'_{11}(R_1)Q_{12}(R_2) - lv_2s_2Q_{22}(R_2)Q'_{21}(R_1) \frac{n_2}{n_1} = \frac{c_1}{n_1}$$

$$-lv_1s_1Q_{11}(R_1)Q'_{12}(R_2) \frac{n_1}{n_2} - lv_2s_2Q'_{22}(R_2)Q_{21}(R_1) = \frac{c_2}{n_2}$$

Proper incentives

- Need to consider institutional arrangements that would encourage nations to recruit sufficiently large registries.
- Proper incentives for efficiency would arise with a system of payments such that whenever a registrant from country j is the only available match for a patient in country k , an external agency would make a payment to country j equal to $v_k l$

Incentives and Voluntary Donations

- The standard (Bergstrom, Blume, Varian) equilibrium model of voluntary contributions does not apply here.
- In that model people donate to public goods for their own benefit. Nobody gets gain from own registration here.
- In that model, different people's contributions are perfect substitutes. Not true here.

A peculiar free rider problem

- It is possible that you could be the only match in the registry for somebody needing a life-saving donation.
- Suppose if you knew this was the case, you would willingly donate.
- But suppose you are not willing to donate if another donor is available.

What would *homo economics* do?

- Calculate the probability that if she makes a donation, she is pivotal (i.e., she is the only one of her type in the registry.)
- Let C be the cost of donating.
- B the value of being a pivotal donator
- V Value of donating if not pivotal.
- Assume $B > C > V$

Meditations of a 'consequentialist' altruist.

- Cares only about effect of her actions.
- No warm glow or social acclaim for belonging to registry if she doesn't donate.
- Will join if and only if she would like to be called if registered.
- Where h is probability of being pivotal, donate iff

$$hB + (1-h)V > C$$

Probabilities of being asked and of being pivotal if asked

	Current Registry		Optimal Registry	
Race	P(Asked Reg) Lifetime	P(Pivotal Asked) h	P(Asked Reg) Lifetime	P(Pivotal Asked) h
Caucasian	.013	.08	.004	.03
Afr-Am	.005	.78	.001	.19
Asian-Am	.006	.30	.002	.11
Hispanic	.008	.22	.003	.08

How generous must you be to donate?

- Suppose $V=0$
- Donate iff $B/C > 1/h$
- For Caucasians this means $B/C > 10$
- For African-Americans $B/C > 4/3$
- Difference arises because Caucasians are much less likely to be pivotal when they donate
- For optimal registry registrants need to be 3 times as generous.

Social acclaim and rewards

- Suppose that you value belonging to the registry, either because of social acclaim or money payments.
- Probably that you are called on in your lifetime is only about 1%.
- May be rational to join registry while planning to refuse if asked.
- In current registry, many registrants don't show up.

Richer Model

- Let π denote the probability a registrant is asked to donate
- Let x denote the money cost of joining the registry
- Let a denote the money value of the social acclaim an individual gains by registering
- Let S denote the shame (net of a) of refusing to donate if asked
- Join if

$$a - x + \pi \max\{h(B - C) + (1 - h)(V - C), -S\} > 0$$

Richer model cont...

- Set $V=0$
- Individual joins the registry if

$$a - x > \pi \min\{C - hB, S\}$$

- i.e., certain benefit is greater than expected shame or expected net cost of donating, whichever is smaller.
- Possibility that person would register and not donate (important)

Paying registrants

- Join iff

$$a - x + r > \pi \min\{C - hB, S\}$$

- Paying people to register increases the number of people willing to register but does not affect decision to donate if asked
- May induce someone we want on the registry to register ($C - hB < S$)
- May induce someone we don't want on the registry to register ($C - hB > S$)

Titmuss Effect

- Join iff

$$a(r) - x + r > \pi \min\{C - hB, S\}$$

- Paying donors reduces social acclaim (a)
 - $a'(r) < -1$
- Johannesen Mellstrom experiment.
- Paying registrants reduces the number of registrants. Probably bad but could be good.

Paying donors

- Join iff

$$a - x > \pi \min\{C - P - hB, S\}$$

- Paying donors reduces cost of donating (or makes it negative)
- May have no effect on decision to register
- Anyone who is induced to join registry by P will donate if asked
- Impact is always GOOD (ignoring Titmuss effect)

Shift in Philosophy

- The NMDP has changed its recruitment strategy in recent years to focus more on recruiting minority donors (numbers of new Caucasian recruits falling since 1996, others rising)
- “Registry has developed to the stage where racial diversity (quality) is a higher priority than recruitment volume (quantity).”
- Some disparity is inevitable.

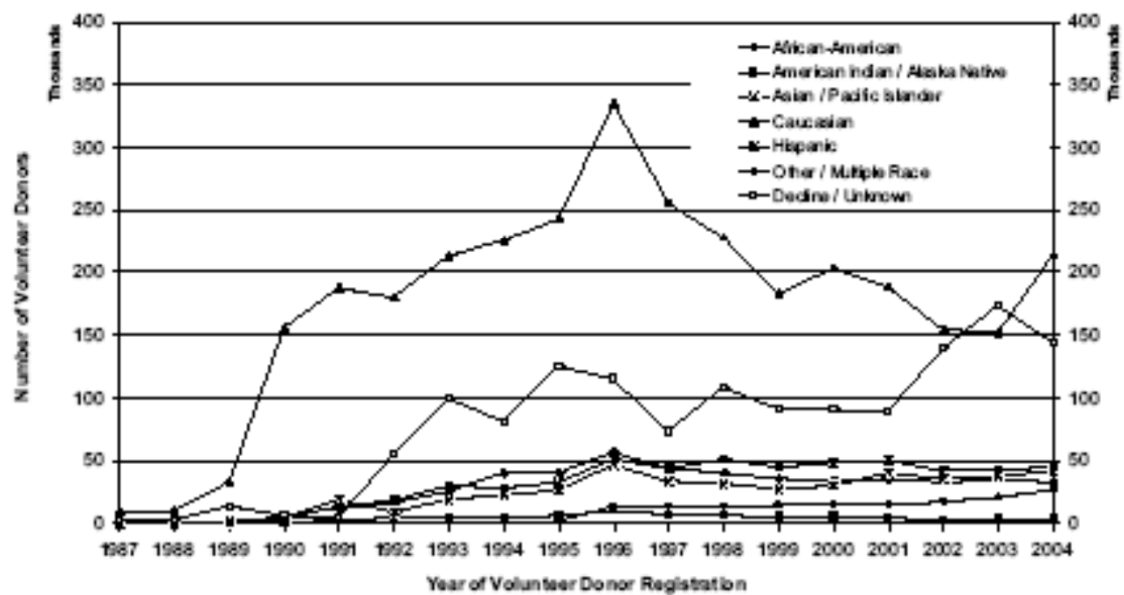


Figure 2-19 Volunteer donor registrations each year by race/ethnic distribution.

Summary

- Current registry has fewer people of all races than is optimal
 - BC ratio highest for Afr.-Am.
 - Optimal registry would include 3 to 10 times more of each race
- Optimal world registry requires international agreements
 - Nash Equilibrium not efficient (too small)
- Need to understand incentives
 - decision to join registry and to donate are separate decisions
 - Social versus financial incentives
 - Paying donors is better than paying registrants