The socioeconomic impact of multiple sclerosis in France: Results from the PETALS study

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Abstract

Background: Multiple sclerosis (MS) places a considerable financial burden on the society. However, data quantifying the contemporary cost burden in France are lacking.

Objective: This cost-of-illness study aimed to estimate the direct and indirect costs associated with MS in France.

Methods: Between October 2020-November 2020, 208 French adults with a confirmed diagnosis of MS were recruited via MSCopilot® (a new MS self-assessment digital solution) and several MS patient networks. Indirect costs were estimated using a combination of top-down and bottom-up approaches. Direct costs were retrieved from Assurance Maladie (i.e. national system of health insurance) publications. Out-of-pocket expenses (OOPEs) incurred by MS patients were also reported. All costs were expressed in €2020. Data from the survey were extrapolated to the overall French MS population.

Results: MS exerted an annual cost burden of €2.7 billion on the French society (indirect costs: €1.3 billion; direct costs: €1.4 billion). Mean annual costs were €27,164.7 per-patient, with indirect and direct costs accounting for 48.1% and 51.9% of the total annual costs, respectively. OOPEs contributed over €90 million to the total annual costs.

Conclusions: MS imposes a substantial cost burden on the French society, with approximately half of the total annual costs driven by indirect costs.

Keywords: direct and indirect costs, France, multiple sclerosis, productivity loss, reduced workforce participation, out-of-pocket expenses

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the present study was undertaken to address the existing gap and estimate the financial burden (direct and indirect) imposed by MS in the French population.

Materials and methods

Study design
This cost-of-illness study used data collected between October 2020 and November 2020 through a patient survey. The survey questionnaire was prepared in collaboration with MS experts at Novartis (Table S1).

Study population
Patients (aged ≥15 years) with a confirmed diagnosis of MS were recruited via MSCopilot® and several MS patient networks across France. MSCopilot® is a new MS self-assessment digital solution developed by Ad Scientiam, which monitors clinically validated digital biomarkers for MS patients and clinicians. Patients with incomplete or inconsistent data were excluded from the study.

Data collection
A patient-based questionnaire consisting of 142 questions was administered to all the enrolled patients via MSCopilot® and email (response rate: 11.9%). Sociodemographic data (age, sex, coverage with private health insurance and long-term illness (i.e. Affection Longue Durée [ALD]), a system by which patients suffering from chronic and/or severe illnesses can benefit from full coverage of care via the French Social Security for the entire duration of their illness), employment status, and annual income at the time of the MS diagnosis and at the time of the survey) were collected. Disease information (time of diagnosis, type of MS, Expanded Disability Status Scale [EDSS] score, and number of relapses since diagnosis and over the past 12 months [if any]) was also collected.

Questions regarding productivity losses covered early exit from the labor market (exclusive of retirement), early retirement (defined as leaving the workforce before the legal retirement age) and increased sick leaves and reduced working time due to MS. The survey also included questions gauging the patients’ perception of benefits or aids available to them (unemployment benefits, minimum income, and health-related benefits such as Allocation adulte handicapé and Majoration pour la vie autonome) as well as income shortfall (i.e. how patients perceived their MS diagnosis to have affected their earning potential). Information on informal care was also collected, where patients were asked whether the caregivers had reduced their working time to provide care. In addition, information related to the number of consultations with medical (physiotherapist, speech therapist, occupational therapist, nurse, and psychologist) and paramedical (hypnotherapist and sophrologist) professionals over the past 3 months was collected.

Costs
Costs were estimated from the societal perspective and consisted of direct medical (consultations with healthcare professionals [HCPs], inpatient and outpatient care, medications, and consumables), direct non-medical (transportation, adapted vehicles, investments/purchases on assistive aids), and indirect (loss of income through reduced employment of both MS patients and caregivers) costs. Data on direct costs were retrieved from Assurance Maladie (i.e. national system of health insurance) publications. Productivity loss was estimated in terms of the proportion of patients prematurely exiting the paid labor market, number of sick leaves, and reduced working time among caregivers attending to a friend or relative with MS. Given the debate surrounding the appropriateness of the human capital approach and the friction cost approach (FCA), a newer, more precise method was developed to monetize productivity loss associated with MS. The new method assumes that there is a possible replacement for every departing worker. Like the FCA, the new method speculates that coworkers compensate for part of the productivity of the absent worker. The concept stems from real inoccupation periods, rather than arbitrary vacancy periods, as commonly used in the literature. For the calculation of costs of permanent exits from the labor market, the average frictional time was assumed to be 8.5 years per job and 4.25 years for early leavers. The recruitment process starts automatically, leading to two scenarios: (i) in 36% of the cases, the recruitment process takes less than 33 days, which leads to zero days of inoccupation and is equal to zero friction cost and (ii) in the remaining 64% of the cases, the recruitment process takes more than 33 days, which leads to a friction period of at least 1 day of position inoccupation. It is assumed that, thereafter, 35 friction laps of 29 days of vacancy occur (35*29 = 1015 working days plus a remainder, which is equal to 4.25 calendar years). The departed worker’s coworkers compensate for 56% of his productivity until a replacement is found. At each lap, the probability that an unemployed worker takes the job and stops the process was considered. For temporary leaves, the
classic FCA was used. All cost estimates were expressed in €2020.

Extrapolation to the French MS population
The answers to the survey questions provided by the patients were extrapolated to the overall French MS population, except for answers where less than 5% of patients had responded. The results of this study are based on cumulative extrapolations of the survey responses and publicly available data.

Statistical analysis
A data management methodology was designed in order to ensure adequate data quality. This enabled the exclusion of questionnaires based on missing/inconsistent data. The analysis was carried out on pseudonymized data, and the results were presented through anonymized and aggregated data. The statistical representativeness of the MS patients included in the survey (N = 206) was determined against the overall French MS population. The representativeness of the sample was tested using the exact binomial test for sex and the χ² conformity test for age and type of MS. Categorical variables are reported as counts and percentages, while continuous measures are summarized as means and standard deviations (SDs). A p value of <0.05 was specified as the threshold for statistical significance. Questionnaire responses were analyzed using R statistical software version 4.0.5.

Ethics
All study data were de-identified and complied with all aspects of the General Data Protection Regulation and therefore were exempted from institutional review board approval.

Table 1. Key characteristics of the survey patients and the French MS population.

|                          | Survey patients (N = 206) | French MS population (N = 101,200) |
|--------------------------|---------------------------|-----------------------------------|
| Mean (SD) age            | 42.3 (10.8)               | 51.0 (NR)                         |
| Age (in years), %        |                           |                                   |
| 15–34                    | 24.3                      | 13.2a                             |
| 35–54                    | 60.7                      | 45.1a                             |
| 55–64                    | 12.1                      | 22.5a                             |
| 65–74                    | 2.9                       | 14.0a                             |
| ≥75                      | 0.0                       | 5.2a                              |
| Female, %                | 78.6                      | 73.0a                             |
| Mean (SD) time since diagnosis, years | 10.2 (8.7) | 14.6 (9.2)a |
| EDSS stages, %           |                           |                                   |
| 1–3                      | 56.8                      | 57.3c                             |
| 4–6                      | 36.4                      | 34.9c                             |
| 7–9                      | 6.8                       | 7.8c                              |
| Affection Longue Durée, %| 96.6                      | 89.0a                             |
| MS phenotype, %          |                           |                                   |
| RMS                      | 70.9                      | 78.8c                             |
| PMS                      | 25.2                      | 13.2c                             |
| CIS                      | -                         | 7.8c                              |
| Do not know              | 3.9                       | -                                 |
| Employment status at diagnosis, % |           |                                   |
| Full-time worker         | 54.9                      | -                                 |
| Student                  | 17.0                      | -                                 |
| Unemployed               | 15.0                      | -                                 |
| (both job seekers and persons out of the labor market) | | |
| Part-time worker         | 8.3                       | -                                 |
| Self-employed            | 4.9                       | -                                 |
| Employment status at the time of the survey, % | | |
| Full-time worker         | 31.6                      | -                                 |
| Unemployed               | 30.6                      | -                                 |
| (both job seekers and persons out of the labor market) | | |
| Part-time worker         | 19.9                      | -                                 |
| Retired                  | 6.3                       | -                                 |
| prematurely due to MS    |                           |                                   |

Abbreviations: CIS: clinically isolated syndrome; EDSS: Expanded Disability Status Scale; MS: multiple sclerosis; NR: not reported; PMS: progressive multiple sclerosis; RMS: relapsing multiple sclerosis; SD: standard deviation.
Source: aAssurance Maladie, 2020; bhttp://www.ofsep.org/fr/9-la-cohorte; cDetournay et al. 2019.

(continued)
Results
Overall, 206 of the 208 patients with MS were included in this study (two patients were excluded; one each due to redundancy and incoherent answers). Among the included patients, 60.7% were recruited via MSCopilot® and the remaining 39.3% were recruited through email.

Patients’ characteristics
The sampled population was younger than the reported French MS population (42.3 vs 51.0 years), but statistically representative in sex distribution (78.6% vs 73.0% of female). The survey patients were more likely to be in ALD (96.6% vs 89.0%) and were comparable in terms of EDSS stages vs the overall French MS population. Most of the respondents reported having relapsing MS (70.9%; Table 1).

Productivity time lost
MS hindered productivity by pushing active employees off the labor market. The employment rate reduced from 80.1% at diagnosis to 64.7% at the time of the survey. The reduction in the employment rate was more prominent among MS patients over 25 years of age (Table 2). Overall, 12 retirees were observed in this sample. Of these, the majority left the labor market early because of MS (n = 11; five aged 35–54 years and six aged 55–64 years). Extrapolation of these results to the French MS population showed that 1800 workers with MS exit the labor market early each year, with 50% exiting early (i.e. without going into retirement) and the remaining 50% retiring early because of MS.

MS also affected the working time of employed patients. Over one-third of the employed patients (38%) reported reduced working time because of MS, which increased with the progression of MS disability (i.e. EDSS 1–3 [n = 77]: 29.9%; EDSS 4–6 [n = 34]: 52.9%; EDSS 7–9 [n = 4]: 75.0%). MS patients were more likely to be working part-time than the overall population of French workers. The proportion of part-time workers increased from 12.1% at diagnosis to 35.7% at the time of the survey. The proportion of patients working part-time increased with age (Figure 1).

In terms of sick leaves, 75.0% of the working patients had taken MS-related sick leaves within 24 months before the survey. The mean duration of sick leaves was 30.3 days. Part-time employees were more likely to report at least one MS-related sick leave in the 24 months preceding the survey (85.4%) compared with their full-time (70.8%) and self-employed counterparts (55.6%). At the population level, 21,014 patients (20.7%) in the total population (n = 101,200) reported taking sick leave due to MS in the past year. MS also affected the income of the workers, with full-time workers with MS earning 17% less than the overall full-time working population in France (Figure 2).

In addition, MS also hindered the productivity of the caregivers. Overall, 14.3% of patients declared that they received help from informal caregivers, thereby affecting caregivers’ working time. Patients with advanced disability were three times more likely to have seen a relative become a caregiver and give up working time (i.e. EDSS 1–3: 9.4%; EDSS 4–6: 17.3%; EDSS 7–9: 35.7%). Similarly, working time lost by caregivers increased with an increase in disability (i.e. EDSS 1–3: 1.7 days/week; EDSS 4–6: 2.3 days/week; EDSS 7–9: 2.8 days/week). Extrapolating these numbers to the French MS population revealed that overall 14,438 caregivers experience reduced working time, equating to 1.5 million days off work annually.

Out-of-pocket expenses (OOPEs)
In general, the number of consultations with HCPs was higher in non-working MS patients (i.e. jobless, retired, or studying) and self-employed workers than in employed MS patients (187.0 vs 50.8). Among employed MS patients, part-time employees were more likely to have consulted HCPs than full-time employees (73.2% vs 69.2%). Approximately half of the MS patients consulted physiotherapists (49.5%), followed by nurses (30.6%) and psychologists (23.3%), whose consultations were not reimbursed by Social Security.

Among the survey patients, 14.4% had purchased adapted vehicles, 43.2% had acquired mobility aids, and 8.7% had received life aids. Approximately a quarter of the patients (23.8%) had purchased MS-related consumables (urine bags, protective equipment, and medical probing equipment). This is driven by the share of patients in EDSS stages 7–9 who had purchased consumables (64.3%). In addition, more than one in 10 patients with at least one dependent child reported that their MS led to extra cost for childcare.

In terms of costs, the mean annual total OOPE per MS patient was estimated at €893.4, translating to an overall annual cost of €90.4 million at the population level. The majority of the OOPEs were driven by
costs due to adapted vehicles (€31.1 million), consultations (€25.1 million), childcare (€16.9 million), and life aids (€13.6 million). The OOPEs were higher in patients in early disability stages (€44.5 million) compared to those with moderate to severe disability (€35.6 million) and very severe disability (€10.3 million) (Table 3).

Annual cost of MS in France
The annual total cost of MS in France was estimated at €2.7 billion, with indirect and direct costs accounting for 1.3 billion and 1.4 billion of the total costs, respectively (Table 3). Costs of health-related aids (€561.5 million), sick leaves (€352.4 million), and productivity loss by caregivers (€274.6 million) were major components of the indirect costs (Table S2). Of the €1.4 billion incurred in direct costs, 86.5% (i.e. €1.2 billion) was borne by the national system of health insurance. Drug costs accounted for most of the direct costs (Table 4). The annual cost per MS patient increased in concordance with their EDSS scores (i.e. €23,967.6 for patients in EDSS stages 1–3; €29,127.7 for patients in EDSS stages 4–6, and €41,556.6 for patients in EDSS stages 7–9). The total annual costs for these groups were €1.4 billion for EDSS stages 1–3, €1 billion for EDSS stages 4–6, and €334 million for EDSS stages 7–9.

Discussion
This study quantified the socioeconomic impact of MS in France. Overall, the results showed that MS exerts an enormous financial burden on the French economy (€2.7 billion per annum), with €1.3 billion incurred in indirect costs and €1.4 billion in direct costs. Loss of income/costs due to reduction in working time contributed over half of the indirect cost (53.3%), followed by health-related aids/benefits (42.5%). Furthermore, OOPEs incurred by MS patients contributed to a notable proportion of the total annual costs (over €90 million).

Understanding the magnitude of the socioeconomic burden posed by MS may provide valuable insights for optimizing resource allocation and devising effective strategies to reduce its impact. Results from the current study showed that MS not only affected the productivity and income of patients but also the working time of caregivers. The patterns of reduced productivity among MS patients and their caregivers are in line with those reported in previous studies and highlight the considerable impact of MS on the professional careers of patients and their caregivers.23,24 Although this study did not investigate the reasons for early retirement, we speculate that they may relate to disease progression in addition to symptoms such as fatigue, cognitive dysfunction, paresthesia, and chronic pain.25,26

Several studies have estimated the cost burden of MS in France; however, the estimates reported were derived using data until 2014.4,5,11,12,27,28 Results from this study showed that MS imposes an annual burden of €2.7 billion. The mean total annual costs were found to vary by MS disability i.e. costs were highest in patients with early disability stages (EDSS 1–3), followed by those with moderate to severe disability (EDSS 4–6) and very severe disability (EDSS 7–9). Estimates from previous studies have reported an annual burden of €586 million (€2004), which increased to €1.2 billion (€2013–€2014).5,11 Taken together, these findings emphasize that the cost burden of MS continues to increase in France despite the availability of newer disease-modifying therapies (DMTs).

Analysis of the total costs revealed that indirect costs (driven by health-related aids, absenteeism, and caregiver costs) accounted for 48.1% and direct costs (drug and hospital care costs) for 51.9% of the total

Table 2. Effect of MS on patients’ employment rate.

| Age      | Employment rate | At the time of survey | French MS population^a |
|----------|-----------------|-----------------------|------------------------|
| <25 years| 16.6%           | 4.3%                  | 7.5%                   |
| 25–49 years| 60.0%         | 45.8%                 | 55.5%                  |
| ≥50 years| 3.5%            | 14.6%                 | 27.5%                  |
| Weighted mean| 80.1%       | 64.7%                 | 90.5%                  |

Abbreviation: MS: multiple sclerosis.
Source: ^INSEE, 2018 (https://www.insee.fr/fr/statistiques/2489589#tableau-figure1_radio2).19
annual costs (€27,164.7 per person per annum). With subtle differences, the direct and indirect costs incurred by MS patients in the present study were largely consistent with those in previously published studies.\textsuperscript{4,11,12} In the study by Kobelt et al., the mean cost per patient from the societal perspective was estimated at €44,400 per annum, with indirect costs accounting for approximately 47% and direct costs accounting for 53% of the annual per-patient cost.\textsuperscript{4} In a retrospective study of insured MS patients (2003–2004), the annual direct and indirect costs per patient (€2004) were found to be €9506 and €12,235, respectively.\textsuperscript{11} Similarly, another retrospective study reported a mean annual cost of €31,500 per patient. Moreover, the cost per patient was found to increase as the disease severity increased. This study also confirmed that while the cost of DMTs contributed to most of the total annual cost in early disease
Table 3. Annual costs\textsuperscript{a} of MS.

|                     | EDSS 1–3 (n = 57,684) | EDSS 4–6 (n = 35,420) | EDSS 7–9 (n = 8096) | Total annual costs (N = 101,200) | Annual cost per patient |
|---------------------|-----------------------|-----------------------|---------------------|----------------------------------|------------------------|
| Total direct costs  | €808.6 million         | €504.7 million         | €117.5 million      | €1.4 billion                     | €14,138.3              |
| Patient OOPE        | €44.5 million          | €35.6 million          | €10.3 million       | €90.4 million                    | €893.4                 |
| Consultations       | €14.3 million          | €8.8 million           | €2.0 million        | €25.1 million                    | €248.3                 |
| Adapted vehicles    | €20.0 million          | €9.6 million           | €1.5 million        | €31.1 million                    | €307.4                 |
| Childcare           | €9.7 million           | €5.9 million           | €1.4 million        | €16.9 million                    | €167.6                 |
| Mobility aids       | €42,732                | €2.1 million           | €402,902            | €2.6 million                     | €25.3                  |
| Life aids           | €0.0                   | €8.7 million           | €4.9 million        | €13.6 million                    | €134.7                 |
| Consumables         | €399,791.2             | €332,140.2             | €47,592.7           | €779,524.2                       | €7.7                   |
| Specialized transportation | €89,620.0   | €78,076.3             | €72,400.7           | €240,097.0                      | €2.4                   |
| Assurance Maladie healthcare costs | €764.0 million | €469.1 million         | €107.2 million      | €1.3 billion                     | €13,244.9              |
| Total indirect costs| €574.0 million         | €526.9 million         | €217.3 million      | €1.3 billion                     | €13,026.5              |
| Loss of income/cost due to reduction in working time | €355.1 million | €254.9 million         | €93.2 million       | €703.2 million                   | €6948.8                |
| Patients            | €43.7 million          | €26.8 million          | €6.1 million        | €76.6 million                    | €757.1                 |
| Employers           | €217.0 million         | €96.3 million          | €14.3 million       | €327.7 million                   | €3238.6                |
| Caregivers          | €80.6 million          | €123.2 million         | €70.8 million       | €274.6 million                   | €2713.2                |
| Assurance Maladie   | €13.8 million          | €8.5 million           | €1.9 million        | €24.2 million                    | €239.9                 |
| Aids/benefits       | €186.4 million         | €252.1 million         | €119.6 million      | €558.1 million                   | €5515.0                |
| Loss of income for patients | €30.5 million | €18.7 million          | €4.3 million        | €53.5 million                    | €528.8                 |
| Total cost by EDSS stage | €1.4 billion     | €1.0 billion           | €334.8 million      | €2.7 billion                     | €27,164.7              |

Abbreviations: EDSS: Expanded Disability Status Scale; MS: multiple sclerosis; OOPE: out-of-patient expense.
Note: \textsuperscript{a}All data presented are mean costs.
with mild disability, costs due to production losses, services, and family contributed largely at later stages with higher EDSS. Despite methodological disparities and differences in components of productivity loss captured between our study and previous studies, these data reinforce the importance of indirect costs, which represent a sizable fraction of the overall costs in MS. Additionally, this study showed that OOPEs contributed over €90 million to the total annual costs of MS, which were mostly driven by medical equipment and devices as well as consultations. When stratified by EDSS stages, OOPEs decreased as the disability increased. Except for mobility equipment costs (which were high for patients with high disability grades, i.e. EDSS ≥ 4), the other components that contributed to the overall OOPEs showed a decreasing trend. The estimated OOPE is substantial given that French MS patients receive full healthcare coverage (ALD). Although the total annual OOPE incurred per MS patient was lower in the present study than in the Heinzlef et al. study (€1500 vs €893.4), it highlights that OOPEs are still daunting and that MS patients in France continue to incur high OOPEs for healthcare services/items not covered by health insurance.

In recent years, several studies have advocated early use of high-efficacy therapies (HETs) being more effective than traditional escalation treatment. In a Danish registry study, relapsing-remitting MS (RRMS) patients directly initiating high-efficacy DMTs had lower risks of 6-month confirmed EDSS worsening and first relapse vs those initiating medium-efficacy DMTs. Evidence from a systematic literature review suggested that early initiation of HETs (i.e. after diagnosis) offers improved control of relapse activity compared with delayed initiation. On similar lines, data from a registry-based study showed that early initiation (i.e. within 2 years of disease onset) of HETs in RRMS patients was associated with lower long-term disability and lower hazard of disability progression compared with delayed initiation (i.e. 4–6 years after disease onset). While these studies endorse the clinical benefits of HETs, we hypothesize that HETs may reduce the financial burden by delaying disease progression, thereby lowering the healthcare costs for MS patients. The results of this study should be interpreted within the context of its limitations. Survey questionnaires were distributed through the MSCopilot® digital application and email, which might have ruled out MS patients not comfortable with digital applications, those having limited/no access to a computer/internet, elderly patients, institutionalized patients, and those with severe MS disabilities. Given that the data were self-reported, the possibility of recall or response biases cannot be ruled out. As the cost estimates were derived from self-reported data, the results need to be interpreted with caution. The indirect cost estimate in this analysis is not exhaustive as it does not account for costs related to home modifications and unpaid leaves (due to a lack of a sufficient sub-sample). The data on OOPEs may be skewed by the underrepresentation of patients with no OOPEs and perception bias. As patients in the ALD system do not pay for consultations or medicines related to their disease, the OOPEs reported in this study are likely underestimated.

In conclusion, our results showed that MS imposes a substantial economic burden on the French society, with indirect costs accounting for almost half of the total annual costs. Furthermore, this study provides valuable insights to policymakers, payers, and HCPs for

Table 4. Annual MS costs incurred by Assurance Maladie.

| Cost category                        | Total annual costs | Cost per patient |
|--------------------------------------|--------------------|------------------|
| Cost due to reduction in working time | €24.3 million      | €239.9           |
| Sick leaves                          | €23.0 million      | €226.7           |
| Early retirement                     | 1.3 million        | €13.2            |
| Benefits                             | €160.2 million     | €1583.6          |
| Direct costs for Assurance Maladie   | €1.2 billion       | €11,661.2        |
| Drugs                                | €712.6 million     | €7041.7          |
| Consultations and out-of-hospital care| €193.6 million     | €1912.7          |
| Hospital care                        | €273.9 million     | €2706.9          |
| Total costs                          | €1.4 billion       | €13,484.7        |

Abbreviation: MS: multiple sclerosis.
Note: All data presented are mean costs.
future healthcare decision-making, particularly with the advent of HETs for the effective management of MS.

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Availability of data and material
The data cannot be made publicly available due to privacy regulations. According to the General Data Protection Regulation, data can only be made available for specific purposes, including research that meets the criteria for access to this type of sensitive and confidential data as determined by a legal review. Readers may contact Alice Bouleau (abouleau@asteres.fr) regarding the data.

Declaration of conficting interests
The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: A Bouleau and CA Schwerer are employees of Asterès. C Dulong, R Delgrange, K Bouaou, T Brochu, and S Zinai are employees of Ad Scientiam. K Švecová is an independent HEOR consultant and has received consulting fees from AOP Orphan, Boehringer Ingelheim, Gilead, Ipsen, Janssen, Kyowa Kirin, Merck, Novartis, Pfizer, Roche and Sanofi. Prof. Sá has received honoraria from Almirall, Bayer Healthcare, Biogen, Bristol-Myers-Squibb, Janssen, Merck, Novartis, Roche, Sanofi Genzyme, and Teva. Prof. Labauge has received honoraria and grants from Novartis, Sanofi Genzyme, Merck, and Roche. A Petropoulos and S Aly are full-time employees of Novartis.

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Supplemental material
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